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ARCHIVES OF OPHTHALMOLOGY

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CHANGES IN THE OCULAR FUNDUS ASSOCIATED WITH PHEOCHROMOCYTOMA OF THE ADRENAL GLAND

Report of Three Cases

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NEW YORK

PHEOCHROMOCYTOMAS are tumors growing from cells of the so-called chromaffin system. They are sometimes referred to as paragangliomas, but Belt and Powell [1] suggested that the former term be used in referring to adrenal growths and the latter to chromaffin tumors of other regions. Chromaffin tissue is present in the adrenal medulla, in the carotid gland, in the organ of Zuckerkandl and in sacrococcygeal and retroperitoneal tissue.

Now, as Raab [2] has shown, the only cells of the adrenal medulla to produce a hormone are the chromaffin cells, or pheochromocytes. They produce epinephrine and related catechols (*o*-dihydroxybenzene), which are similar to epinephrine though not identical with it, but which enhance its effect. According to Cannon,[3] there is no excretion without stimulation, such as exercise, emotion or drugs. Plasma taken during a crisis has been found to have a pressor effect. Paragangliomas can produce hypertension, and MacKeith [4] found that in 9 of 13 cases the offending tumor was in the retroperitoneal tissues.

PATHOLOGIC CHARACTER

Scholl and his collaborators [5] stated that these tumors are usually benign, but Padis [6] expressed the opinion that a tumor which if left to

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1. Belt, A. E., and Powell, T. O.: Clinical Manifestations of Chromaffin Cell Tumors Arising from Adrenal Medulla: Suprarenal Sympathetic Syndrome, Surg., Gynec. & Obst. **59**:9-24 (July) 1934.

2. Raab, W.: The Pathogenic Significance of Adrenalin and Related Substances in the Heart Muscle, Exper. Med. & Surg. **1**:188 (May) 1943.

3. Cannon, W. B.: The Adrenal Medulla, Bull. New York Acad. Med. **16**: 3-13 (Jan.) 1940.

4. MacKeith, R.: Adrenosympathetic Syndrome: Chromaffin Tissue Tumor with Paroxysmal Hypertension, Brit. Heart J. **6**:1-12 (Jan.) 1944.

5. Scholl, A., and others: Review of Urologic Surgery, Arch. Surg. **48**:325-354 (April) 1944.

(Footnotes continued on next page)

itself may kill the patient cannot be so considered. Baumgarten and Cantor [7] considered them benign anatomically, but malignant physiologically. However, malignant forms appear and have been reported by Ausbittel and Holtz,[8] Lazarus and Eisenberg,[9] Cahill,[10] McGavack and his collaborators,[11] King,[12] Knabe,[13] Bonnamour and his collaborators [14] and others. As Eisenberg and Wallenstein [15] have pointed out, these malignant forms are usually bilateral and are not, as a rule, responsible for increased output of epinephrine; but in the cases of McKenna and Hines,[16] Langeron and Delcour,[17] Schröder [18] and numerous others the malignant growth was associated with hypertension.

The pheochromocytoma is usually small, rarely exceeding the size of a walnut. Wells and Boman [19] stated that the largest known tumor weighed 1,000 Gm., but they had apparently overlooked Borch-Johnsen's [20] tumor, which weighed just twice as much. Most cases

6. Padis, N.: Paroxysmal Hypertension Caused by Adrenal Tumor, Clinics **4**:87-96 (June) 1945.

7. Baumgarten, F. C., and Cantor, M. O.: Pheochromocytoma: Case Report, Ann. Surg. **111**:112-116 (Jan.) 1940.

8. Ausbittel, F., and Holtz, B.: Unusual Clinical Aspects of Bilateral Medullary Tumor of Adrenal Gland, Med. Klin. **36**:1016-1020 (Sept. 13) 1940.

9. Lazarus, J. A., and Eisenberg, A. A.: Paraganglioma of Adrenal: Two Cases, J. Urol. **27**:1-26 (Jan.) 1932.

10. Cahill, G. F.: Hormonal Tumors, Surgery **16**:233-265 (Aug.) 1944.

11. McGavack, T. H.; Benjamin, J. W.; Speer, F. D., and Klotz, S.: Malignant Pheochromocytoma of Adrenal Medulla (Paraganglionoma): Report of Case Simulating Carcinoma of Adrenal Cortex with Secondary Adrenal Insufficiency, J. Clin. Endocrinol. **2**:332-338 (May) 1942.

12. King, E. S. J.: Malignant Pheochromocytoma, J. Path. & Bact. **34**:447-452 (July) 1931.

13. Knabe, E.: Bilateral Pheochromocytoma of the Adrenal: Significance of Epinephrine for Clinical Picture of These Tumors, Virchows Arch. f. path. Anat. **308**:615-628, 1942.

14. Bonnamour, S.; Doubrow, and Montegue: Pleural Metastasis of Paraganglioma of Adrenal Gland, Ann. d'anat. path. **4**:141-146 (Feb. 3) 1927.

15. Eisenberg, A. A., and Wallenstein, H.: Pheochromocytoma of Adrenal Medulla (Paraganglioma): Clinicopathologic Study, Arch. Path. **14**:818-836 (Dec.) 1932.

16. McKenna, C., and Hines, L.: Paraganglioma of Suprarenal Gland, J. Urol. **34**:93-86 (Aug.) 1935.

17. Langeron, L., and Delcour, J.: Relation of Adrenal Tumors to Arterial Hypertension, Arch. d. mal. du cœur **21**:13-18 (Jan.) 1928.

18. Schröder, K.: Unusual Bilateral Chromaffin Tumors of the Adrenal Gland Case, Virchows Arch. f. path. Anat. **268**:291-299, 1928.

19. Wells, A. H., and Boman, P. G.: Clinical and Pathologic Identity of Pheochromocytoma of Adrenal Gland: Report of Case, J. A. M. A. **190**:1176-1180 (Oct. 9) 1937.

20. Borch-Johnsen, E.: Operated Case of Paraganglioma Gland Suprarenal. Sin. Associated "with the Suprarenal Sympathetic Syndrome," Acta chir. Scandinav. **80**:171-179, 1937.

occur in the second, third and fourth decades of life, but there are wide variations. Linde's [21] patient was 5 months old, and Eisenberg and Wallenstein [15] found a case of a patient aged 82.

Microscopically, the tumor is a recognizable reproduction of the chromaffin cells, and the cytoplasm takes a dark stain. The growth has a glandular appearance, due to the tendency of the cells to be arranged around a central lacuna.

BIOLOGIC ASSAY

Numerous biologic assays of excised pheochromocytoma tissue have been performed. Because the normal content of epinephrine in the blood as estimated by Barr [22] is only 1 : 10,000,000, direct measurement is technically no easy task; but, through work on cats' denervated irises and rabbits' sympathectomized ears, certain relative values have been obtained. According to Kalk,[23] the normal adrenal gland contains 1 to 2 mg. of epinephrine per gram of tissue. The epinephrine content of pheochromocytoma tissue has been found to vary from 1 mg. (Kelly and associates[24]) to 30 or 40 mg. per gram (Kalk[23]). A common method of estimation of the epinephrine content is to compare the effect of a known quantity of tumor tissue with that of a known quantity of epinephrine (Brunschwig and associates [25]). Mencher [26] reported that each gram of tumor caused a reaction in the cat's denervated iris equal to 8 mg. of epinephrine, and Duncan and his collaborators [27] estimated that the tumor had a pressor activity equal to 210 mg. of epinephrine. Strömbeck and Hedberg [28] found that the epinephrine content of the blood was thirty times the normal between crises and one thousand

21. Linde, P.: Unusual Tumor (Pheochromocytoma) in Infant Five Months Old, Nord. med. (Hygiea) **13**:897-898 (March 21) 1942.

22. Barr, P.: Recent Advances in Endocrinology, J. A. M. A. **105**:1760 (Nov. 30) 1937.

23. Kalk, H.: Paroxysmal Hypertension: Study of Blood Pressure Crises in Presence of Tumor of Medulla, Klin. Wchnschr. **13**:613-617 (April 28) 1934.

24. Kelly, H. M.; Piper, M. C.; Wilder, R. M., and Walters, W.: Paroxysmal Hypertension with Paraganglioma of Right Suprarenal Gland, Proc. Staff Meet., Mayo Clin. **11**:65-70 (Jan. 29) 1936.

25. Brunschwig, A.; Humphreys, E., and Roome, N.: Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma of Adrenal Gland, Surgery **4**:361-370 (Sept.) 1938.

26. Mencher, W. H.: Paroxysmal Hypertension Caused by Pheochromocytoma: Adrenalectomy, J. Mt. Sinai Hosp. **10**:743-746 (Jan.-Feb.) 1944.

27. Duncan, L. E., Jr.; Semans, J. H., and Howard, J. E.: Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus: Disappearance of Diabetes After Removal of Tumor, Ann. Int. Med. **20**:815-821 (May) 1944.

28. Strömbeck, J. P., and Hedberg, T. P.: Tumor of Adrenal Medulla Associated with Paroxysmal Hypertension: Report of Case Preoperatively Diagnosed and Cured by Extirpation After Capsular Excision, Acta chir. Scandinav. **82**: 177-189, 1939.

times the normal during an attack. Free epinephrine has been found in tumors by most observers, but none could be demonstrated by Biskind and his co-workers.[29] Methods used in assaying the tumors have been described by Brunschwig and his collaborators,[25] Langeron and Lohéac [30] and numerous other authors.

HISTORY AND OCCURRENCE

Pheochromocytoma of the adrenal gland was first described by Fränkel [31] in 1886. In those days the tumor was usually observed at postmortem examination, and little clinical progress was made for more than thirty years. According to Padis,[6] only 3 cases have been recorded in the Lankenau Hospital in Philadelphia and 3 cases in the Johns Hopkins Hospital, in the last seventy-five years. Kirschbaum and Balkin [32] found 3 in 14,437 consecutive cases in the Cook County Hospital, in Chicago.

Pheochromocytoma was recognized as a clinical entity in 1922 by Labbé and his co-workers [33] and firmly established as such by Vaquez and Donzelot [34] in 1926. The first case in which the diagnosis was made prior to operation was that of Pincoffs [35] in 1929. This tumor was removed surgically by Shipley.[36]

Pheochromocytoma has been considered a rare tumor, but it is being detected with increasing frequency of late. For example, up to 1939 Brunschwig and Humphreys [37] had collected 103 cases. In the next

29. Biskind, G. R.; Meyer, M. A., and Beadner, S. A.: Adrenal Medullary Tumor: Phaeochromocytoma Cured by Surgical Intervention; Clinical Management; Analysis of All Reported Operated Cases, J. Clin. Endocrinol. **1**:113-123 (Feb.) 1941.

30. Langeron, L., and Lohéac, P.: Amount of Epinephrine in Tumors Removed at Necropsy: Significance in Pathogenesis and Pathogenic Mechanism of Arterial Hypertension, Presse méd. **36**:1153-1155 (Sept. 12) 1928.

31. Fränkel, F.: Bilateral Adrenal Tumor: Report of a Case, Virchows Arch. f. path. Anat. **103**:244-263, 1886.

32. Kirschbaum, J. D., and Balkin, R. B.: Adrenalin Producing Pheochromocytoma of Adrenal Associated with Hypertension: Report of Three Cases, Ann. Surg. **116**:54-60 (July) 1942.

33. Labbé, M.; Tinel, J., and Doumer: Solar Crises and Paroxysmal Hypertension Associated with a Tumor of the Adrenal Gland, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982-990 (June 23) 1922.

34. Vaquez, H., and Donzelot, E.: Crises of Paroxysmal Arterial Hypertension, Presse méd. **34**:1329-1331 (Oct. 23) 1926.

35. Pincoffs, M. C.: A Case of Paroxysmal Hypertension Associated with Adrenal Tumor; abstracted, Tr. A. Am. Physicians **44**:295-299 (May) 1929.

36. Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of Adrenal Gland, Ann. Surg. **90**:742-749 (Oct.) 1929.

37. Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, J. A. M. A. **115**:355-357 (Aug. 3) 1940.

five years, according to the figures of Kvale and his collaborators,[38] 17 had been added. In the last two years about 26 additional cases have appeared in the literature. In fact, more than 16 per cent of all cases have been reported in the last two years. The tumor is probably not becoming commoner, but it is certainly being detected more frequently.

SYMPTOMS

First of all, it should be remembered that there may be no symptoms at first, and hypertension may be discovered by accident. Later, symptoms may be produced by excitement, stress, worry, changes in position, pressure on the abdomen or neck, hyperventilation (Mortell and Whittle[39]) or even voluntarily, as in the case reported by Porter and Porter.[40] Sometimes malaise or parasthesias appear as premonitory symptoms. According to MacKeith,[4] all symptoms arise from (*a*) recurrent paroxysms of generalized hypertension, (*b*) chronic hypertension with renal and cardiac failure or (*c*) involvement of the cortex of the adrenal gland (such as Addison's or Cushing's disease).

Hypertension is a constant symptom. It is paroxysmal at first but may be continuous, as pointed out by Cahill,[10] Lukens[41] and others. Sometimes the pressures are very high. In Strickler's[42] case there were readings of 330 systolic and 150 diastolic, but in most cases the pressure is about 200 systolic. The paroxysmal phase is not permanent. As Mencher (in his discussion on the paper by Hyman and Mencher[43]) pointed out, the hypertension soon becomes permanent. A similar observation was recorded by Baumgarten and Cantor[7] and several others. The hypertension may last for days, or even months (Edward[44]), and acute paroxysms may last from several minutes to several days. According to MacKeith,[4] the average duration of an attack is two hours.

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38. Kvale, W. F.; Roth, G. M.; Claggett, O. T., and Dockerty, M. B.: Headache and Paroxysmal Hypertension: Observations Before and After Surgical Removal of Pheochromocytoma, S. Clin. North America **24**:922-933 (Aug.) 1944.

39. Mortell, E., and Whittle, J.: Pheochromocytoma: Case Report, with Certain Observations on Pathologic Physiology, J. Clin. Endocrinol. **5**:396-402 (Nov.) 1945.

40. Porter, M. F., and Porter, M. F., Jr.: Report of Case of Paroxysmal Hypertension Cured by Removal of Tumor, Surg., Gynec. & Obst. **50**:160-162 (Jan., no. 1 A) 1930.

41. Lukens, F. D. W.: Diagnosis and Treatment of Disorders of Adrenal Glands, M. Clin. North America **26**:1803-1815 (Nov.) 1942.

42. Strickler, C. W., Jr.: Pheochromocytoma: Operative Failure; Case Report, South. Surgeon **11**:193-200 (March) 1942.

43. Hyman, A., and Mencher, W. H.: Pheochromocytoma of Adrenal Gland, J. Urol. **49**:755-776 (June) 1943.

44. Edward, D. G. F.: Phaeochromocytoma of Adrenal Gland and Hypertension, with Details of Case, J. Path. & Bact. **45**:391-403 (Sept.) 1937.

Allen's [45] patient was under observation for sixteen years, and in Hamilton's [46] case a ten year recession supervened. Thoracic pain of the anginal type is frequent. Between attacks the patient may feel well, although hypertension may persist. Sometimes this may fall to normal for a while (van Goidsenhoven and Appelmans [47]).

Other symptoms include lacrimination and salivation, hemoptysis (MacKeith [4]), diarrhea (Shipley [36]), pain in the hypochondrium and sweating (Kvale and his collaborators,[38] Crane and his collaborators [48] and Duncan and associates [27]). Van Epps and his co-workers [49] listed, in addition, such symptoms as sensations of fulness and pressure in the neck, pallor followed by flushing, cyanosis of the nail beds, angiospasm of the extremities and the tip of the nose, tachycardia (occasionally bradycardia), forceful cardiac impulse, nervousness, muscular weakness, air hunger, tinnitus, vertigo and nausea.

During attacks the urine may be either plentiful or scanty to the point of anuria; albumin and casts may be found. According to Vaquez and Donzelot,[34] the latter may be due to small renal hemorrhages produced during the paroxysms. Between attacks the urine is normal, until definite renal damage supervenes.

Glycosuria and hyperglycemia are reported in a great number of the cases, and the diabetes disappears when the tumor is removed (Duncan and associates,[27] Biskind and his collaborators [29] and others). Sometimes the glucose readings are very high; in Strickler's [42] case, for example, the fasting blood sugar was 283 mg. per hundred cubic centimeters. That some diabetic patients had been harboring an unsuspected tumor was shown by Duncan and associates,[27] who cited cases of Herde, Kelly, Biebl, Wichsel, Rogers and de Wesselow. In all of them the patients had been treated for diabetes, and in all pheochromocytomas were observed at autopsy. Other cases of glycosuria were reported by Van Epps and his co-workers [49] (273 mg. of glucose

45. Allen, P. L.: Chromaffin Cell Tumor Associated with Paroxysmal Hypertension, Texas State J. Med. **36**:540-542 (Dec.) 1940.

46. Hamilton, J. E.: Pheochromocytoma of Adrenal with Paroxysmal Hypertension: Case Relieved by Surgery, Kentucky M. J. **38**:572-575 (Dec.) 1940.

47. van Goidsenhoven, F., and Appelmans, R.: Paroxysmal Hypertension of Adrenal Medullary Origin: Clinical and Therapeutic Study, Bull. Acad. roy. de méd. de Belgique **14**:672-694, 1934.

48. Crane, J. J.; Abson, L. A., and Touriel, E. L.: Tumor of Medulla of Adrenal Gland Associated with Paroxysmal Hypertension: Case Preoperatively Diagnosed and Cured by Surgical Removal, J. Urol. **46**:1100-1102 (Dec.) 1941.

49. Van Epps, E. F.; Hyndman, D. R., and Greene, J. A.: Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of Adrenal: Report of a Proved and of a Doubtful Case, Arch. Int. Med. **65**:1123-1129 (June) 1940.

per hundred cubic centimeters), Landau and associates,[50] Ausbittel and Holz [6] and others.

In nondiabetic cases, the blood picture is not greatly affected, but increased lymphocytes were reported by MacKenzie and McEachern,[51] Hatieganu and associates [52] and others.

In many cases the basal metabolic rates have been greatly increased, often in association with diabetes. In Strickler's [42] case the basal metabolic rate was + 74 per cent; in McCullagh and Engel's,[53] + 36 per cent, and in Binger and Craig's,[54] + 61 per cent. Other signs of hypermetabolism are not necessarily present. Just as the diagnosis of diabetes mellitus is sometimes made in cases of pheochromocytoma, so are the symptoms occasionally ascribed to hypermetabolism. In fact, in the case reported by Brunschwig and Humphreys [37] an operation had previously been performed for thyrotoxicosis, apparently without deleterious effect. Here, again, successful removal of the adrenal tumor is followed by a fall in the basal metabolic rate. In Hyman and Mencher's [48] case it fell from + 69 to — 17 per cent, and in Evans and Stewart's [55] case, from + 43 and + 48 to — 13 and — 17 per cent, respectively. Similar cases have been reported by Rabin [56] and others.

Since Raab [2] has shown that epinephrine in the blood is absorbed by heart muscle, the electrocardiographic findings are of interest. They have been analyzed by MacKeith.[4] During attacks there were found auricular premature beats; tachycardia; bradycardia; arrhythmia; slurring of the QRS complex; left axis deviation, and inverted, flattened or elevated T waves. Between attacks the electrocardiograms in one third of the cases were normal. Of the others, large P waves were present in 3 cases, but left axis deviation and diminution or inversion of the T waves were usual.

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50. Landau, A.; Paszkiewicz, L.; Slavinski, Z., and Steffen, E., Jr.: Grave Paroxysmal Hypertension in Patient with Paraganglioma of the Adrenal Gland: Clinical Study, with Particular Reference to Diagnosis, Rev. belge sc. méd. **8**:330-343 (May) 1936.

51. MacKenzie, D. W., and McEachern, D.: Tumor of Adrenal Medulla (Pheochromocytoma), with Removal and Relief of Paroxysmal Hypertension, J. Urol. **40**:467-476 (Oct.) 1938.

52. Hatieganu, I.; Moga, A., and Radu, P.: Changes in Blood Picture (Lymphocytosis) During Hypertensive Crises Due to Paraganglioma of Adrenal Gland, Zentralbl. f. inn. Med. **61**:337-344 (May 25) 1940.

53. McCullagh, E. P., and Engel, W. J.: Pheochromocytoma of the Adrenal Gland with Hypermetabolism: Two Cases, Ann. Surg. **116**:61-75 (July) 1942.

54. Binger, M. W., and Craig, M. M.: A Typical Case of Hypertension with Tumor of Adrenal Gland, Proc. Staff Meet., Mayo Clin. **13**:17-20 (Jan. 12) 1938.

55. Evans, W. F., and Stewart, H. J.: Peripheral Blood Flow in Case of Adrenal Pheochromocytoma Before and After Operation, Am. Heart J. **24**:835-842 (Dec.) 1942.

56. Rabin, C. B.: Chromaffin Cell Tumor of Suprarenal Medulla (Pheochromocytoma), Arch. Path. **7**:228-243 (Feb.) 1929.

Pheochromocytoma of the adrenal gland is so often associated with other pathologic changes that it is difficult to separate the original symptoms from those of accompanying diseases and complications, and other findings are therefore discussed under the head of differential diagnosis. Mortell and Whittle [39] accounted for the wide variations in symptoms by the supposition that the active principle secreted by a pheochromocytoma may not be the same in all cases, a statement which is admittedly conjectural. When death occurred, it was found to have been immediately due to one of many causes, most frequently acute pulmonary edema, shock, cerebral hemorrhage or chronic renal failure. Oberling and Jung's [57] patient died in labor; Hick's [58] had a subarachnoid hemorrhage, and Stevens and Waite's [59] had a ruptured thoracic aorta. Other cases of rapid or sudden death were reported by Dolgin [60] and Holtz.[61] No cause of death was found in Cabot's [62] case.

OPHTHALMOLOGIC FINDINGS

In order to obtain some idea of the ocular changes in patients with this tumor, I examined all available case reports published in the last twenty years. There were many duplications. These were sometimes caused by an author's reporting the same case more than once, sometimes alone, sometimes with a collaborator. For example, a case reported by MacKeith [4] was reported again by Broster and MacKeith,[63] and at least 1 of Engel, Mencher and Engel's cases [64] was reported twice. Sometimes the same case appeared under a different authorship.

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57. Oberling, C., and Jung, G.: Paraganglionoma Causing Fatal Obstetric Shock: Case, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:366-371 (March 24) 1947.

58. Hick, F. K.: Suprarenalin-Producing Pheochromocytoma of Suprarenal Gland: Report of a Case, Arch. Path. **15**:665-674 (May) 1933.

59. Stevens, B. F., and Waite, W. W.: Pheochromocytoma of Adrenal Gland: Case Report with Autopsy Findings, Texas State J. Med. **35**:469-471 (Nov.) 1939.

60. Dolgin, W.: Pheochromocytoma of Right Adrenal and Sudden Death Following Injury of Head: Case with Autopsy, Arch. Path. **40**:135-140 (Aug.) 1945.

61. Holtz, E.: Sudden Death of Patient with Pheochromocytoma of Adrenal Gland, Deutsche Ztschr. f. d. ges. gerichtl. Med. **32**:94-108, 1939.

62. Arteriosclerosis: Ganglion Neuroma of Adrenal, Cabot Case 17091, New England J. Med. **204**:447-453 (Feb. 26) 1931.

63. Broster, L. R., and MacKeith, R.: Adrenosympathetic Syndrome (Pheochromocytoma with Paroxysmal Hypertension) with Transposition of Viscera, Brit. J. Surg. **31**:393-395 (April) 1944.

64. Engel, F. L.; Mencher, W. H., and Engel, C. L.: "Epinephrine Shock" as Manifestation of Pheochromocytoma of Adrenal Medulla: Report of Case with Successful Removal of Tumor, Am. J. M. Sc. **204**:649-661 (Nov.) 1942.

Kalk's [23] case, for instance, was also reported by Buchner,[65] and Pincoffs' [35] case, by Shipley.[36] Furthermore, it seemed advisable to omit the cases of malignant tumors with no hypertension, although those with hypertension were included. Eventually, 108 suitable cases were collected. When these were examined, it was found that in only 38 of them was there any mention of ocular signs or symptoms. This, of course, does not indicate that in the remaining 70 cases an ophthalmologic examination was not made; it means merely that no mention of such an examination was included in the report. For example, Cahill [10] noted in the body of his paper that vascular changes occur in the eyes. He had found it necessary to omit such details from his protocols. Sometimes an internist, in reporting the eyes as normal, was referring only to the external appearance. In support of this, the paper of McCullagh and Engel [53] may be cited. In the report of 1 case, they stated that the eyes were normal; but, in discussing the same case, they noted the presence of "eyeground changes of essential hypertension, grade I to II." Moreover, in the cases in which the fundi were called normal, it was not indicated whether or not the ophthalmoscopic examination was performed by an ophthalmologist. Many internists use the ophthalmoscope well, but small irregularities in the lumens or other slight changes might easily elude them. Sometimes examination was not feasible—all 3 of Kirschbaum and Balkin's [32] patients, for example, were comatose, and failure to perform ophthalmoscopic examinations is understandable. However, Van Epps and his collaborators [49] gave no details of the visual acuity or findings in the fundus in a case in which vision was poor before operation and improved afterward.

In all, the fundi were reported to have been normal in 12 cases—the cases of Padis [6] (2 of 3 cases), Stevens and Waite,[59] Bensis and Codonnis,[66] Strickler,[42] Hamilton,[46] Kelly and his co-workers,[24] Landau and his co-workers,[50] Kalk,[23] MacKenzie and McEachern [51] and Soffer and his collaborators (2 cases).[67]

In the 26 cases in which pathologic changes were found in the eyes, the descriptions were not always sufficiently detailed to serve as a guide to the pathologic process present. Visual acuity was seldom recorded, and terminology was by no means standard. It was not always clear whether spastic vessels were observed during or between attacks, and renal function at the time of examination was often not

65. Buchner, F.: Specific Tumors (Pheochromocytoma) of Adrenal Medulla with Hypertension: Report of Two Cases, Klin. Wchnschr. **13**:617-619 (April 28) 1934.

66. Bensis, W., and Codonnis, A.: Paroxysmal Hypertension Due to Medullosuprarenoma: Report of Case, Bull. Acad. de méd., Paris **121**:237-256 (Feb. 21) 1939.

67. Soffer, L.; Mencher, W., and Colp, R.: Symposium on Surgical Diagnosis of Pheochromocytoma: Two Cases with Operative Removal, S. Clin. North America **26**:368-381 (April) 1946.

noted. The condition of the vessels immediately after operation was never mentioned, and the time of return of the fundi to normal was not stated. In only 1 case (Engel, Mencher and Engel [64]) was the posture noted at the time of examination. Nevertheless, a composite picture of the pathologic changes in the eye will be clear to the careful reader (table).

In all the cases in which the eyes showed abnormalities the arteries were found to be narrowed. In 9 of these cases only the vessels were affected. In 5 of the 9 cases the type of constriction was not noted (Allen,[45] Beer and his collaborators,[68] McCullagh and Engel [53] and Duncan [27] and Thorn [69] and their associates); but in 2 of the 4 remain-

Incidence of Pathologic Changes in the Eye in Cases of Pheochromocytoma of the Adrenal Gland Reported Since 1927

			Number	(per Cent) of Cases
Cases of pheochromocytoma			106	
Cases in which ocular examination was noted			38	(35%)
Normal eyes			12	(32%)
Pathologic changes in eyes			26	(68%)
Vascular changes without retinopathy				
Narrowing (unspecified)	5			
Narrowing (spastic)	2			
Narrowing with blurring of disks	2			
		9	(35%)	
Vascular changes with retinopathy				
Hemorrhage only	3			
Exudate only	1			
Hemorrhage and exudate	1			
Retinal and optic nerve atrophy	1			
Papilledema, hemorrhage and exudate	9			
		15	(58%)	
Probable lesion of fundus		2	(7%)	

ing cases (Engel and his collaborators [64] and Wells and Boman [19]) spastic vessels and, in addition, blurring of the margins of the disks were present. Of the 15 cases in which retinopathy was found, retinitis of the so-called albuminuric type, with cotton wool patches, optic neuritis and hemorrhage, was present in 9 (Holst [61] [2 cases], Evans and Stewart,[55] Palmer and Castleman,[70] Brenner and his collaborators,[71]

68. Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma of the Adrenal Gland with Demonstration of Pressor Substance (Adrenal or Epinephrin in Blood Preoperatively During Hypertensive Crises), Ann. Surg. **106**:85-91 (July) 1937.

69. Thorn, G. W.; Hindle, J. A., and Sandmeyer, J. A.: Pheochromocytoma of Adrenalin Associated with Persistent Hypertension, Ann. Int. Med. **21**:122-130 (July) 1944.

70. Palmer, R. S., and Castleman, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of Adrenal Gland Simulating Malignant Hypertension: Report of Case, New England J. Med. **219**:793-796 (Nov. 17) 1938.

Hoffmeyer,[72] Biskind and his collaborators,[29] Rodin[73] and deVries and his collaborators[74]). Hemorrhage alone was noted in 3 cases (Kvale and associates,[38] Coller and co-workers[75] and Binger and Craig[54]); exudate alone was noted by Evans.[76] Retinal and optic nerve atrophy was observed by Kremer.[77] Cases in which there was probably a pathologic condition of the fundus, but in which no examination was described, were reported by Mayo[78] and Van Epps and his co-workers.[49]

It is interesting to note that in Holst's[61] first case the severe changes were not present four weeks before the diagnosis was made. In Kremer's[77] case ocular changes were present two years before the diagnosis was established. In Evans'[76] case severe retinal lesions occurred in the absence of renal impairment, not an unusual finding. In Biskind's[29] case a "remarkable diminution in hemorrhage and exudate" occurred in the seven months following operation. In the case reported by de Vries and his co-workers,[74] there were found papilledema, arteriovenous compression, hemorrhages and exudate. Ten days after removal of the tumor the papilledema had become less pronounced. In two months the hemorrhages had absorbed, and in five months the papilledema had likewise disappeared. The white areas, which the authors stated to be degenerative, were still present seven months later.

For reasons already set forth, these figures show too many variables to permit their statistical use, but certain conclusions can be drawn. When the eyes of patients with pheochromocytoma of the adrenal gland were examined, 68 per cent showed pathologic changes; of eyes in which a pathologic process was found, 100 per cent showed vascular constric-

71. Brenner, F.; Konzett, H., and Nagl, F.: Pheochromocytoma of Adrenal Gland with Concomitant Neurofibromatosis: Report of Case, München. med. Wchnschr. **85**:914-916 (June 17) 1938.

72. Hoffmeyer, J.: Two Forms of Adrenal Tumor and Their Possible Relation to Arteriosclerosis, Virchows Arch. f. path. Anat. **302**:627-639, 1938.

73. Rodin, F. H.: Hypertensive Retinopathy Associated with Adrenal Medullary Tumor (Pheochromocytoma), Arch. Ophth. **34**:402-407 (Nov.-Dec.) 1945.

74. de Vries, A.; Mandl, F.; Rachmilevitz, M., and Ungar, H.: Paroxysmal Hypertension Due to Medullary Tumor (Pheochromocytoma): Successful Operation, Surgery **19**:522-529 (April) 1946.

75. Coller, F. A.; Field, H., Jr., and Durant, T. M.: Chromaffin Cell Tumor of Adrenal Causing Paroxysmal Hypertension, Relieved by Operation, Arch. Surg. **28**:1136-1148 (June) 1934.

76. Evans, V. L.: Suprarenal Tumor with Paroxysmal Hypertension: Case Report, J. Lab. & Clin. Med. **22**:1117-1120 (Aug.) 1937.

77. Kremer, D. N.: Medullary Tumor of Adrenal Glands, with Hypertension and Juvenile Arteriosclerosis, Arch. Int. Med. **57**:999-1007 (May) 1936.

78. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve: Report of Case, J. A. M. A. **89**:1047-1050 (Sept. 24) 1927.

tion, and 35 per cent showed lesions severe enough to be classified as albuminuric retinitis.

The best description of these fundi in the literature is that of Rodin,[78] but his claim that they represent a "new clinical entity" is invalidated by the fact that they had been described in a score of papers before the publication of his report, in 1945.

DIAGNOSIS

It has already been seen how the frequent coexistence of an increased basal metabolic rate and of hyperglycemia and glycosuria can prove misleading in arriving at a diagnosis of pheochromocytoma of the adrenal gland. How difficult this may be has been pointed out by Padis [6] and by Palmer and Castleman.[70] The commonest erroneous diagnosis seems to have been "essential hypertension" (hypertensive vascular disease), and because there were often pathologic findings in the urine during attacks it was believed that renal insufficiency had supervened. In the differential diagnosis, MacKeith [4] noted that in hypertensive vascular disease the paroxysms are gradual and the blood pressure remains high between attacks. Widespread symptoms are rare and are not easily precipitated by pressure, changes in posture or other excitants. It is imperative to keep in mind the urgency of early diagnosis. As Mencher (in his discussion on Hyman and Mencher [43]), Baumgarten and Cantor [7] and many others have pointed out, the hypertension becomes permanent after a while, and the blood pressure remains elevated between attacks. It has already been noted, and will be described later, how the effect of the disease on the retina offers an equally strong argument for early diagnosis.

Symptomatic paroxysmal hypertension may also occur with lead poisoning, eclampsia, tabes, angina pectoris, tumor of the thalamus, disorders of the vagus nerve and Nothnagel's syndrome.[79] The disease has also simulated gastric ulcer, shock, migraine and cerebral tumor (MacKeith [4]). Furthermore, the syndrome has frequently been associated with other diseases. Evangelesti's [80] patient had hemocytoblastoma (undifferentiated cell leukemia). Rosenthal and Willis [81] and others reported the coexistence of tuberculosis, and, of course, syphilis is

79. This syndrome is characterized by coldness and numbness of the extremities, sweating, hypertension and bradycardia. It was first reported eighty years ago but was discussed and evaluated by Lewis (Heart **15**:305-327 [July] 1931).

80. Evangelesti, T.: Pheochromocytoma of Adrenal Gland in Case of Acute Hemocytoblastic Leukemia: Anatomicopathologic Study, Arch. "de Vecchi" per anat. pat. e med. clin. **1**:492-508, 1939.

81. Rosenthal, D. E., and Willis, R. A.: Association of Chromaffin Tumors with Neurofibromatosis, J. Path. & Bact. **42**:499-603 (May) 1936.

sometimes encountered (Labbé [82]). Diagnosis was made difficult in the case reported by Heath and his co-workers [83] by the concurrence of menopausal symptoms. Barker's [84] patient had delusions and hallucinations, and these symptoms were also apparent in a patient under the observation of Perkins.[85] In the case reported by Mortell and Whittle [39] convulsive seizures occurred.

It is remarkable how often other tumors are found in conjunction with pheochromocytoma. The commonest associated condition is neurofibromatosis. This association was observed in cases reported by Rosenthal and Willis,[81] Kirschbaum and Balkin,[82] Russum and Barry [86] and others. In fact, Eisenberg and Wallenstein [15] collected 5 such cases (up to 1932), and in 1938 Brenner and his collaborators [71] found 8 cases of neurofibromatosis among 64 cases investigated. Other tumors reported are cystadenoma of the pancreas, hypernephroma (carcinoma) of the kidney (which was contralateral to the pheochromocytoma), adenoma of the liver, colloid adenoma of the thyroid gland (Eisenberg and Wallenstein [15]) and sarcoma of the mediastinum (Russum and Barry [86]). In Lazarus and Eisenberg's [9] case carcinoma of the thyroid gland was present, and in the case reported by Lengeron and Delcour,[17] carcinoma of the esophagus. Sometimes a mixed type of tumor seems to involve the adrenal cortex (either by extension or coincidentally), and associated symptoms suggestive of Cushing's syndrome (pituitary basophilism) have been reported by Hantschmann,[87] LeCompte [88] and others. According to Cahill,[10] the positive diagnosis depends on (*a*) a typical paroxysmal attack, (*b*) clinical evidence that the attacks are produced by a pressor substance, (*c*) demonstration of the pressor substance in the blood and (*d*) roentgenologic evidence of the tumor on perirenal insufflation. The last procedure has aroused a great deal of

82. Labbé, M.: Adrenal Tumors Causing Paroxysmal Arterial Hypertension, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1535-1537 (Dec. 3) 1934.

83. Heath, F. K.; Cahill, G. F., and Atchley, D. W.: Pheochromocytoma of the Adrenal Gland: Correct Diagnosis and Successful Operation, J. A. M. A. **117**:1258-1260 (Oct. 11) 1941.

84. Barker, L. F.: Cystic Tumor of Medulla of Suprarenal Gland (Paraganglioma), Associated with Early and Persistent Arterial Hypertension, With Arterial Thickening and With Multiple Hemorrhages Within Central Nervous System, Causing Epileptiform Convulsions, Paralyses, and Psychopathic State, M. Clin. North America **14**:265-268 (July) 1930.

85. Perkins, O.: Personal communication to the author.

86. Russum, B. C., and Barry, M. W.: Paraganglioma in Suprarenal Medulla with Neurofibromatosis, Nebraska M. J. **15**:243-244 (June) 1930.

87. Hantschmann, L.: Tumors of the Adrenal Gland Associated with Hypertension, Klin. Wchnschr. **20**:394-398 (April 19) 1941.

88. LeCompte, P. M.: Cushing's Syndrome with Possible Pheochromocytoma: Report of Case, Am. J. Path. **20**:394-398 (April 19) 1941.

discussion. Cahill,[10] whose experience is wide, stated that he prefers it; and it was recommended by Scholl and his co-workers [5] and many others. Mencher [43] has carried out the procedure more than one hundred times without mishap. Crane and his co-workers,[48] MacKeith [4] and others stated the belief that it was dangerous, and de Vries and his collaborators [74] recommended tomography. Fish (in his discussion on Roome [89]) suggested the substitution of oxygen for air. According to MacKeith,[4] the mass can be palpated in one third of the cases.

Chemical studies of the blood may be used in establishing the diagnosis. Following a suggestion credited by them to McQuarry, Wells and Boman [19] advocated estimating the serum potassium during an attack. This suggestion was based on the fact that intravenous injection of epinephrine may produce an increase in blood potassium of as much as 86 per cent. In MacKeith's [4] case the potassium measured 46 mg. per hundred cubic centimeters. (The normal values are from 16 to 20 mg. per hundred cubic centimeters.)

Treatment consists in surgical removal of the tumor. The operation is a serious one, but the deaths are increasingly less frequent of late. Here, again, statistics are hard to evaluate, as some of the patients died after operation and follow-up observations are not always given. At present, a rough estimate would put the chances of recovery at about 70 per cent.

Accounts of successful removal of the tumor may be found in the articles already cited; cases are also discussed in the papers of Volhard [90] and Suermondt.[91] Case reports analyzed, but not specifically cited in the text, are to be found in the papers of Fingerland,[92] Hahn,[93] Rømcke,[94] Nettleship,[95] Borras and Meyer Mota[96] and Laubry and Bernal.[97] Excellent reviews have been presented by Bianchi [98] and

89. Roome, N.: Visualization of Adrenal Glands by Air Injection, J. A. M. A. **111**:1061-1065 (Sept. 17) 1939.

90. Volhard, F.: Paroxysmal Hypertension Due to Medullary Tumor: Operation Followed by Recovery, München. med. Wchnschr. **91**:120 (March 10) 1944.

91. Suermondt, W. F.: Paroxysmal Rise in Blood Pressure Cured by Removal of Tumor, Zentralbl. f. Chir. **61**:70-74 (Jan. 13) 1934.

92. Fingerland, A.: Pheochromocytoma of the Adrenal Gland: Report of Two Cases, Virchows Arch. f. path. Anat. **309**:218-234, 1942.

93. Hahn, P.: Pheochromocytoma of the Adrenal Gland: Report of Case, Schweiz. med. Wchnschr. **72**:622-627 (June 6) 1942.

94. Rømcke, O.: Paroxysmal Hypertension Due to Pheochromocytoma: Case, Nord. med. (Norsk mag. f. lægevidensk.) **12**:2953-2956 (Oct. 18) 1941.

95. Nettleship, A.: Medullary Tumor of the Adrenal Gland: Chromaffin Cell Tumor, J. Clin. Endocrinol. **1**:124-125 (Feb.) 1941.

96. Borras, P. E., and Meyer Mota, M.: Paraganglioma: Case, Semana méd. **1**:990-994 (May 5) 1938.

97. Laubry, C., and Bernal, P.: Paraganglioma of Adrenal Medulla: Case, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:658-661 (May 21) 1934.

Tanzella.[99] Discussions are to be found in the reports of Broster,[100] Gartner,[101] Barlaro,[102] Labbé and his co-workers,[103] Peyron[104] and Langeron and his collaborators.[105] A symposium on the subject will be found under the names of Lian, Seguier and Girauld[106] and Welti.[107]

REPORT OF CASES

CASE 1.—J. L., a girl aged 12, was admitted to the Babies Hospital on Sept. 2, 1943, complaining of excessive perspiration and failure to gain weight for the last two years. The family and past histories were noncontributory. She had been well until two years prior to admission, when the parents noted that she perspired profusely. The sweating was accompanied with polyphagia and polydipsia, but there was no polyuria. The child became intolerant of heat and refused covers even on cold winter nights. The parents maintained that she had not gained weight in the past two years and that during the few weeks before admission she had lost several pounds. The patient had recently complained of her heart beating fast, but no dyspnea or other cardiac symptom was noted. The child had not been as active as previously. The parents noticed no tremor or exophthalmos. The basal metabolic rates, determined on two occasions two weeks before her admission, were reported to have been + 50 and + 30 per cent.

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98. Bianchi, A. E.: Paraganglioma of Adrenal Gland (Pheochromoblastoma), An. Inst. modelo de clín. méd. **20**:361-392, 1939.

99. Tanzella, A.: Adrenal Tumors and Hypertension: Review of Literature, Riv. di clin. med. **37**:663-669 (Oct. 15-30) 1936.

100. Broster, L. R.: Tumors of Adrenal Gland, Practitioner **144**:135-142 (Feb.) 1940.

101. Gartner, W.: Clinical Picture, Especially Circulatory Disorders, in Paraganglioma, Ztschr. f. Kreislaufforsch. **28**:82-90 (Feb. 1) 1936.

102. Barlaro, P. M.: Relation of Cardiovascular Diseases and Endocrine Diseases: Hypertension Associated with Adrenal Tumors, Prensa méd. argent. **19**:331-337 (July 25) 1932..

103. Labbé, M.; Violle, P. L., and Azerad, E.: Medullary Adenoma of Adrenal Gland with High Epinephrine Content and Paroxysmal High Blood Pressure (Gilbert Dreyfus), Hôpital **18**:472-474 (July) 1930. Labbé, M., and Nepveux, F.: Paroxysmal Hypertension of Adrenal Origin: Case, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:337-347 (March 5) 1934.

104. Peyron, A.: Paraganglioma and Its Cardiovascular Syndrome, Bull. Assoc. franç. p. l'étude du cancer **19**:618-650 (July) 1930.

105. Langeron, L.; Paget, M., and Lohéac, P.: Estimation of Epinephrine in Tumors: Relation to Histologic Structure of Tumor and Blood Pressure of Subject; Three Cases, Compt. rend. Soc. de biol. **100**:873-875 (April 8) 1929.

106. Lian, C.; Seguier, F., and Girauld, A.: Diagnostic Possibilities of Questioning Patient with Common Forms of Paroxysmal Arterial Hypertension Due to Paraganglioma, Semaine d. hôp., Paris **22**:7 (Jan. 7) 1946; Paradoxic Circulatory Collapse and Sudden Death in Course of Paroxysmal Arterial Hypertension Due to Paraganglioma, ibid. **22**:7-10 (Jan. 7) 1946; Paroxysmal Arterial Hypertension Due to Paraganglioma: General Survey, ibid. **22**:1-3 (Jan. 7) 1946.

107. Lian, C.; Welti, H., and Seguier, F.: Paroxysmal Arterial Hypertension Due to Paraganglioma: Case, Semaine d. hôp., Paris **22**:3-6 (Jan. 7) 1946. Welti, H.: Surgical Treatment of Paroxysmal Arterial Hypertension Due to Paraganglioma, ibid. **22**:13-15 (Jan. 7) 1946.

The patient was well developed but thin; the skin was warm and moist, with little subcutaneous fat. The temperature was 100 F., the pulse rate 108, the respiratory rate 24 and the blood pressure 180 systolic and 120 diastolic in the left arm and 210 systolic and 150 diastolic in the left leg. The thyroid was not enlarged but was palpable. There were no nodules or swelling. The heart was not enlarged; the rate was rapid; the sounds were of good quality, and there were no murmurs. The liver was palpable 2 cm. below the costal margin. The remainder of the physical examination revealed nothing abnormal.

Results of laboratory tests were as follows: hemoglobin, 96 per cent; white blood cells, 8,850; polymorphonuclear leukocytes, 62 per cent; lymphocytes, 38 per cent. The urine showed a faint trace of albumin and an occasional white blood cell. The tuberculin test gave a negative reaction. The fasting blood sugar was 88 mg. and the nonprpotein nitrogen 34.6 mg., per hundred cubic centimeters. Creatine-creatinine studies showed a ratio of creatine to total creatinine of about 0.4 The serum iodine was 4.8 micrograms per hundred cubic centimeters (normal value for girls of this age, 6.2 micrograms per hundred cubic centimeters). The basal metabolic rates were + 51.1 and + 56.8 per cent on successive days. The blood pressure was taken by a number of observers and was always in the range of the original reading. The blood pressure when the patient was sitting or standing was much lower than when she was lying down. It was raised by immersion of the limbs in ice water, was lowered by pressure on the abdomen and was unaffected by pressure on the carotid artery. Injection of 0.2 cc. of epinephrine hydrochloride (1 : 1,000) intravenously produced immediate subjective complaints of headache and nausea; the blood pressure rose sharply after administration but returned to initial levels in twenty minutes. The patient was discharged without final diagnosis, and on two subsequent admissions little change in her condition was found except that on one occasion the blood pressure was found to be 240 systolic and 150 diastolic and the basal metabolic rate + 67 per cent.

The patient was readmitted on Aug. 3, 1944. In the interval her condition had remained unchanged. Results of an intravenous pyelographic examination showed that the pelves and calyxes were normal except for slight ectasis of the left pelvis. A flat roentgenogram of the abdomen showed that the renal and adrenal shadows were not clearly outlined. In the region of the shadow of the left adrenal gland there was a single, small shadow of the density of calcium. On August 14 both flanks were injected with air. The kidneys were found to be well outlined, but there was considerable enlargement in the region of the left adrenal gland in both the immediate and the twenty-four hour roentgenogram. On August 17 an exploration of the left adrenal gland was made by Dr. George F. Cahill, with excision of the tumor of the left adrenal gland. After the operation the temperature rose to 104.6 F. but quickly fell to normal. The wound healed satisfactorily, and on the twenty-third postoperative day the patient was discharged. There was no significant drop in her blood pressure, which was 172 systolic and 144 diastolic at the time of her discharge, on Sept. 9, 1944.

The pathologist, Dr. A. P. Stout, reported that the tumor was a pheochromocytoma.

The patient was readmitted on Oct. 4, 1944 because her blood pressure had not fallen below 174 systolic and 140 diastolic and it was felt that residual epinephrine-producing neoplastic tissue had been left behind. On October 10 the patient was given intravenous injections of the benzodioxane drugs 1164 F. (dimethyl-2,4-piperidinomethylbenzodioxane) and 933 F (piperidylmethyl benzodioxane). The former, which has an adrenolytic and a sympatholytic action, was used because it

had been controlled by experiments on patients with hypertensive vascular tissue, in whom it uniformly failed to lower the blood pressure. The blood pressure was lowered in the present case. It was considered that the hypertension exhibited by the patient was caused by excessive amounts of circulating epinephrine. On October 13 an attempt was made to assay the patient's blood for epinephrine by measuring its effect on the blood pressure of a cat. The experiment failed to reveal the presence of epinephrine in her blood but indicated that the blood contained a factor which had a lethal effect on the cat.

On October 19 an exploration of the retroperitoneal space was carried out by Dr. Cahill. A tumor was encountered cephalad and mesial to the left adrenal gland in the retroperitoneal space and was removed. After operation, the blood pressure fell to a level of 138 systolic and 100 diastolic. The patient was symptomatically much improved. There were cessation of excessive diaphoresis and absence of headache and palpitation. She was discharged on the sixteenth postoperative day.

The pathologic report of the excised tumor, by Dr. M. M. Melicow, stated that the characteristics were essentially those of the original tumor.

Since the second operation the patient has done well. When last seen, on April 7, 1946, her blood pressure was 116 systolic and 78 diastolic, her pulse rate 92 and her weight 92½ pounds (42 Kg.), and she was entirely devoid of symptoms.

Ophthalmic Study.—The eyes were examined on July 1, 1944, by Dr. James McGraw. The margins of the disks were blurred, and there was at least 1 D. of elevation. The arteries were conspicuously narrowed, and areas of scattered spasm were seen. There was slight arteriovenous notching. Nasal to the right disk were several fluffy white exudates, and to the left lay a small, flame-shaped hemorrhage. The peripheral fields were normal and the blindspots perhaps a little enlarged. Vision was 20/20 in each eye. On September 9 the same observer noted that there had been considerable visual loss, the vision now being reduced to 20/70 in the right eye and 20/40 in the left eye. The fundi were approximately the same as before. On October 11 star-shaped exudates were observed between the disk and the macula. The hemorrhages had been absorbed, but the arteries had become more tortuous. In the meantime, however, the papilledema had increased to 3 D. Vision was 20/40 in the right eye and 20/50 in the left eye. Dr. McGraw's impression on this occasion was that the process had reached the stage of hypertensive retinopathy grade III. On October 24, Dr. McGraw noted that there was no perceptible change in the appearance of the fundi.

On November 22, a month after the second operation, the vision had increased to 20/30 in the right eye and 20/20 in the left eye. The papilledema had nearly subsided. Notes as to the spasticity of the arteries, unfortunately, were not made on this occasion. On Oct. 8, 1945, vision was 20/20 in each eye. The retinopathy had almost entirely cleared, and the spasm of the blood vessels had completely disappeared. An occasional exudate was seen around the maculas. When she was last seen, on April 2, 1946, the vision and fundi were entirely normal.

Case 2.—D. B., a 10 year old Negro girl, was admitted to Babies Hospital on Feb. 20, 1946. For three years the child had had nervous attacks and episodes of perspiration. The present illness was first noticed when, on walking up a hill to school, the child would become extremely nervous, exhausted and breathless and would complain of a pain in the epigastrium. She would vomit and the mother would put her to bed, at which time the child was sweating profusely. After she had calmed down, she was apparently as well as before. The mother expressed

the belief that the attacks were correlated with emotional factors rather than with physical exertion; for example, the child could climb the stairs at home without being exhausted. The attacks occurred every week, and for two years the mother took the child to a clinic. There no definite diagnosis was made, but the child was carried as an outpatient without treatment except for advice about resting and diet. The physician there found the blood pressure to be low. The child continued to have attacks at home, and sometimes at school, until she was seen by a cardiologist, who found an enlarged heart on fluoroscopic examination and advised admission to another hospital. She was hospitalized elsewhere three or four months later and remained there until admitted to the Babies Hospital. The symptoms had not changed during this period. While in the other hospital, she underwent a benzodioxane test. The blood pressure, both systolic and diastolic, fell 50 mm. and remained depressed for ten minutes.

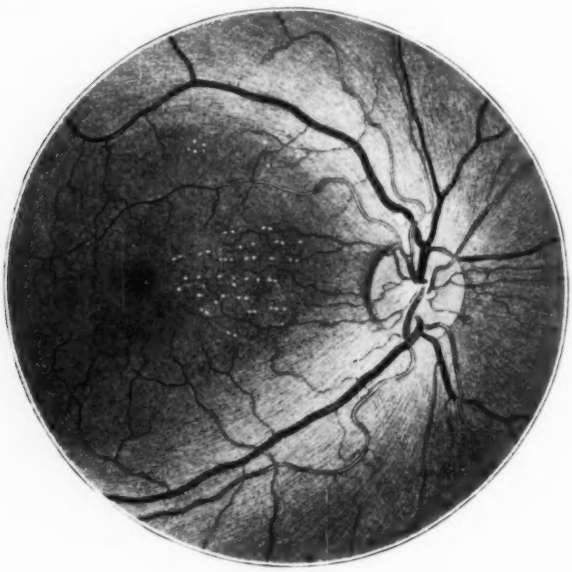

Fig. 1.—Fundus in case 2.

Physical examination showed that the child was well developed and well nourished and in no apparent discomfort. The skin was dry and slightly scaly over the back and front of the chest. Her throat was clear, and the tonsils were small. Several small submaxillary lymph nodes were found. The chest was symmetric, and there was no precordial bulge. The heart was slightly overactive; the impulse was moderately forceful, and there were no thrills. Sounds over the base were of good quality. The second pulmonic sound was slightly louder than the second aortic sound. Over the lower part of the precordium every other first sound was heard as a bit softer. The pulse rate was 96 per minute. Over the apical region there was a soft, slow, blowing systolic murmur, localized to a small area. There were occasional extrasystoles. Pulsation of the femoral artery was easily felt. The blood pressure was 182 systolic and 130 diastolic in the right arm and 180 systolic and 130 diastolic in the left arm. The abdomen was soft and was slightly tender in the upper left and middle quadrants on deep palpation. There was no

apparent tenderness in the costovertebral angle. The edge of the liver was palpable, but no tumor was felt. The blood pressure readings taken with massage of the abdomen were as follows: Left side: base line reading, 186 systolic and 146 diastolic; readings at one minute intervals, 192, 202, 210, 198, 194 and 182 systolic and 148, 150, 160, 148, 146, and 136 diastolic. Right side: base line reading, 176 systolic and 122 diastolic; at ten seconds, 178 systolic and 130 diastolic; at one minute, 182 systolic and 134 diastolic; at two minutes, 182 systolic and 132 diastolic; at three minutes, 180 systolic and 130 diastolic. Special examinations of the heart, including electrocardiographic and roentgenographic studies, revealed the following signs: a prominent bulge in the cardiac shadow in the left ventricle without evidence of enlargement of the left auricle, pulsus alternans, occasional extrasystole and sinus tachycardia.

An aerogram of the adrenal glands showed no definite enlargement. A roentgenogram of the upper part of the genitourinary tract showed the lumbar portion of the spine to be normal. The outlines of the psoas muscle were distinct. Both kidneys could be partially visualized: The right appeared normal in size, shape and position; the left was somewhat enlarged and appeared to be lower than normal. A roentgenogram of the lower part of the genitourinary tract revealed nothing abnormal. An intravenous pyelogram showed good function bilaterally. Laboratory tests revealed the following values: hemoglobin, 12.2 Gm. per hundred cubic centimeters, or 84 per cent; red blood cells, 4,390,000, and white blood cells, 13,400, with 73 polymorphonuclear leukocytes. The urine was normal. The nonprotein nitrogen was 30.6 mg. per hundred cubic centimeters. The serum sodium measured 131 mg. and the serum potassium 4.5 mg., per hundred cubic centimeters. The sedimentation rate was 13 mm. in one hour. The reaction to the Kline test was negative.

The patient was in the hospital for thirty days, during which time the blood pressure showed a wide fluctuation, the systolic ranging from 150 to 250 and the diastolic from 90 to 150 mm. Such variations were independent of external stimuli. Episodes of diaphoresis and nervousness continued. The pulse rate fluctuated from 100 to 120 per minute. The temperature was constantly normal. Pulsus alternans continued, and the cardiac reserve appeared to be gradually diminishing. On the thirtieth day after the patient's admission, using tribromoethanol solution U.S.P. induction and ether anesthesia, Dr. Cahill made an exploration of the adrenal glands. No tumor was observed in the right adrenal. A small, palpable, rounded mass was observed retroperitoneally on the right side, apparently at the bifurcation of the aorta. A mass, the size of a large orange, was noted in the right epigastric area. This was deep red and was covered with cirsoid, dilated veins. The slightest touch of this mass was accompanied with a notable increase in the rate and volume of aortic pulsation. The mass was seen to extend backward along the vertebra, deep into the right lateral vertebral space. It was independent of the kidney and the adrenal gland. Every attempt to handle the mass was accompanied with alterations in the pulse, as determined in the abdominal aorta. The anterior veins were ligated doubly and incised; at this period the patient's pulse ceased. Attempts were made to stimulate the heart, which apparently was in contraction. Artificial respiration was given, but the patient died.

The pathologist, Dr. C. H. Lynch, reported a pheochromocytoma. Autopsy, performed by Dr. Beryl H. Paige, revealed that between the adrenal glands and the upper poles of the kidneys was a tumor 5 cm. in its greatest diameter. The anterior surface of this mass was soft and friable and blood stained in places, and pale yellow in others. The myocardium of the left verticle was greatly hypertrophied, but the cusps of the aortic valve were normal. No definite nephritis was demonstrated.

Ophthalmic Examination.—Prior to the patient's admission, the following note had been made: "Examination of the fundi revealed arteriolar spasm with 'silver wire' veins; there was no papilledema, hemorrhage or exudate." On Feb. 26, 1944, she was examined by Dr. J. P. Macine. He found the disks somewhat hyperemic but fairly distinct. Physiologic excavations were present. There was generalized narrowing of the arterioles, with banding, tortuosity and increased reflexes. Notching of the veins was present. There was beginning formation of a star between the disk and the macula in the right eye. No hemorrhages were seen.

Case 3.—P. D., a boy aged 12 years, was admitted to the Babies Hospital on Oct. 4, 1946, with the complaint of failure of vision for one week. The family history was irrelevant. The patient had had two convulsions in infancy, one at 12 months and the other at 15 months of age, each occurring during a febrile infection of the upper respiratory tract. He had had chickenpox and measles. A gangrenous appendix was removed in 1942, and the same year he had been struck on the top of the head by a thrown brick, receiving a severe laceration of the scalp. The following year he had been thrown from a horse, and in 1945 he had been hit above the left eye by a golf ball, with resulting laceration.

One week before admission the patient began to complain of poor vision, saying that the objects in the room were blurred and that he could not read large print in books. He was examined on the day of admission by his ophthalmologist, Dr. R. N. Berke, who found papilledema, hemorrhages and exudate in both eyes. The patient had been noted to have excessive diaphoresis and thirst during the previous three years, symptoms associated with emotional crises resulting from such events as acting as altar boy in church. Symptoms had become severer during the past summer. About two years before he began to have episodes ushered in by severe, pounding headache, which was quickly associated with generalized constant aching abdominal pain, nausea, vomiting, sometimes pallor and "pounding heart." These symptoms occurred about once a month, lasted a day or so and were followed by another day or two of weakness, diaphoresis and loss of appetite. Attacks were precipitated, it seemed, by excitement or anticipation of an event such as a boy scout hike, school play or confirmation; and almost invariably he became so ill that he was unable to participate in the event. No attacks occurred from June 1946 until the present episode. A blood pressure reading taken by a nurse in June, during an interval of freedom from the symptoms, was reported as "normal."

During the month before his admission the patient seemed to tire easily and was weak on arising in the morning. On admission, he appeared to be well nourished and well developed; he was ambulatory, did not seem acutely ill, was mentally alert, cooperative and pleasant and was apparently of normal intelligence. The temperature was 99 F., the pulse rate 80, the respiratory rate 24 and the blood pressure 260 systolic and 190 diastolic in both the arms and the legs. Examination of the heart showed that the point of maximum impulse was in the fifth interspace, about 1 cm. to the left of the nipple line. It was forceful and easily visible. No enlargement of the heart was apparent on percussion. The aortic second sound was very loud, louder than the second pulmonic sound. No murmurs were heard. The lungs appeared clear on percussion and auscultation. The abdomen was soft, and the liver, kidney and spleen were not felt. No masses were palpated except for feces in the left lower quadrant. There was a well healed scar at McBurney's point, and no tenderness was elicited. The genitalia were normal and prepubescent.

The laboratory findings were as follows: hemoglobin, 15 Gm. per hundred cubic centimeters; red blood cells, 5,500,000; white blood cells, 17,800; polymorpho-

nuclear cells, 41 per cent; lymphocytes, 52 per cent; monocytes, 5 per cent; eosinophils, 1 per cent; basophils, 1 per cent. The Schilling count was as follows: no myelocytes, 9 stab forms and 33 mature neutrophils; there was no stippling. Examination of the urine showed a p_H of 6, a specific gravity of 1.010 and absence of albumin, sugar and acetone; amorphous material was revealed on microscopic examination. Subsequent urinalysis revealed an occasional mixed cast. Chemical analysis of the blood showed nonprotein nitrogen, 37.2 mg.; sugar, 99 mg.; serum albumin, 5.34 Gm., and globulin 2.72 Gm., per hundred cubic centimeters. The sedimentation rate was 14 mm. in one hour. The reaction to the subcutaneous injection of 0.01 mg. of old tuberculin was negative.

On Oct. 14, 1946, a roentgenogram of the skull revealed no visible abnormalities. A roentgenogram of the knees on October 5 revealed no abnormalities and no

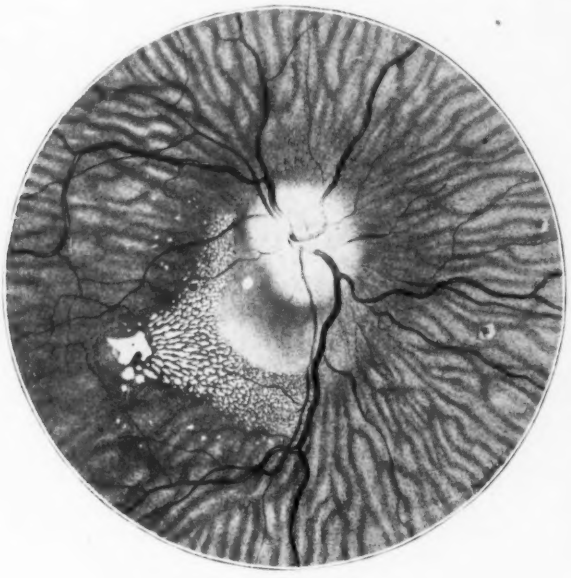

Fig. 2.—Fundus in case 3.

evidence of renal osteodystrophy or generalized rarefaction. There was a cortical defect on the medial aspect of the shaft of the femur. No roentgenologic evidence of calcification was seen in the region of the adrenal glands. The heart shadow was small. An aerogram on October 10 showed diffusion of air about both kidneys, but no enlargement of the adrenal gland was demonstrated on either side. The right kidney was somewhat small. An aerogram of the right side on October 12, forty-eight hours later, showed that the renal area was still not distinct, but there was possibly slight enlargement of the adrenal gland. Two shotlike areas of increased density were lying to the left of the spine. An intravenous pyelogram (October 16) showed a hypoplastic right kidney.

An electroencephalogram (October 7) showed "bursts of high voltage, 3 per second activity appearing synchronously in all leads, and transient focal signs in the right parietal area." An electrocardiogram (October 14) showed "left axis deviation and prolonged conduction."

The patient's physical findings and complaints did not change until the third day in the hospital, when he began to have episodes of generalized abdominal pain, associated with severe pounding headache, pallor, sweating, nausea, vomiting and retching. During the most violent of these attacks his pulse was 140 and his blood pressure 270 systolic and 210 diastolic. The abdomen was not palpated during these episodes because of the possibility of pheochromocytoma. Intravenous injection of magnesium sulfate did not seem to affect the blood pressure. On the fifth day in the hospital the blood pressure had dropped to 168 systolic and 134 diastolic. His acute symptoms had subsided, and he was pale, listless and unwilling to eat. A recording of his blood pressure after the injection of 12 mg. of a benzodioxane derivative showed a drop to 138 systolic and 110 diastolic fifty-five seconds after injection, with almost immediate return to the original level of 162 systolic and 128 diastolic. On the eighth day in the hospital the blood pressure had dropped to 118 systolic and 82 diastolic, and the first aerogram was taken by Dr. Cahill, showing the left kidney to be well delineated but the right kidney to be surrounded with air only over the lower pole. On the ninth day in the hospital the patient was noted to be reading the "funny books." He was alert and free from all complaints.

On the sixteenth day in the hospital cystoscopic examination, made with the patient under anesthesia, revealed that the bladder and ureters were normal. A pyelogram indicated hypoplasia of the right kidney. A second aerogram of the right side showed that the renal area was still not distinctly seen. On the twenty-third day in the hospital the patient was up and moved about with ease, without complaint. The blood pressure ranged from 120 systolic and 100 diastolic to 170 systolic and 100 diastolic. On the twenty-sixth day in the hospital he was taken to the operating room; with tribromoethanol solution–nitrous oxide and oxgen induction, with supplementary anesthesia induced with intravenous injection of "pentothal sodium," the abdominal cavity was opened by Dr. George F. Cahill. It was observed that the left kidney was enlarged and that the left adrenal gland was not remarkable; the right kidney was hypoplastic and exhibited a mass about 5 by 5 cm., with a fibrous capsule attached to the renal pedicle and overlying the vena cava. The right adrenal gland was not remarkable. The right kidney and the attached mass were excised. During the entire procedure the blood pressure remained relatively stable and exhibited no untoward rise or decline. A continuous intravenous drip of isotonic sodium chloride solution U.S.P. was maintained during the latter half of the operation, and 500 cc. of whole blood was given by transfusion. The immediate postoperative condition was good.

Immediately after the operation, and for the succeeding three days, the temperature was 101 to 103 F. and then suddenly fell to normal and remained so. The patient was given a course of injections of penicillin, 20,000 units intramuscularly every three hours during this period. Except for this febrile episode, the postoperative course was uneventful. The blood pressure remained about 120 systolic and 80 diastolic. On the ninth postoperative day, another trial of a benzodioxane derivative was given intravenously, with the blood pressure ranging from 118 to 124 systolic and 90 to 100 diastolic. There was no significant fall or rise after the drug (0.6 cc.) had been given. The surgical wound healed well, and the urine was normal. The patient was up and about for a week prior to his discharge, during which time he was without complaint, ate well and gained weight. He was discharged, in good condition, on the fourteenth postoperative day, or the fortieth day in the hospital.

The pathologist, Dr. M. M. Melicow, made the report of pheochromocytoma of aberrant adrenal medullary tissue.

Ophthalmic Examination.—I examined the patient's eyes on Oct. 5, 1946, when they appeared externally normal. In the right eye, the nerve head was somewhat pale and striated, and the papilledema measured 3 to 4 D. There was an area of exudate between the edematous disk and the macula, arranged roughly in the form of an inverted fan, so that the apex was centered on the macula. This exudate was rather fluffy in appearance, but the macula itself was occupied by a dense white plaque, which was slightly refractile. A small hemorrhage was seen just nasal to the disk. At the periphery two minute areas of old choroiditis were observed. The arterioles were greatly narrowed, and the arteriovenous ratio was about 1 : 2. This narrowing was largely uniform, although in places, notably along the course of the inferotemporal artery at the edge of the edematous disk, there was almost complete occlusion. The light reflex was not notably increased, but there was distinct denting of the veins with no definite sclerotic phenomena at the crossings.

In the left eye, the findings were essentially the same except that the macula seemed to have escaped and no chorioretinal lesions were observed. The child was in bed and ill, and no attempt was made to determine the visual fields or to measure the visual acuity.

I saw the patient again on October 9, on which occasion he was much better and his blood pressure had temporarily fallen to 140 systolic. At this examination I got the impression that the arteries were somewhat larger, and the arteriovenous ratio was approximately 2 : 3. On October 14 the blood pressure was 120 systolic. On this occasion I noted that the hemorrhage had been absorbed and the vessels were definitely larger. The exudate was of about the same extent but less fluffy in appearance, and was, indeed, beginning to resemble that seen in diabetic retinopathy. The papilledema was unchanged. The vessels were definitely larger, and there was no evidence of spasticity. Vision was 20/200 in the right eye and 20/50 in the left eye, unimproved by correction. The visual field in the left eye showed a normal periphery, but the right eye showed considerable defect in the inferonasal sector.

The patient was next seen on Nov. 4, 1945, at which time the hemorrhage was absorbed, the papilledema was subsiding and the exudate, while perhaps somewhat diminished, showed no decided change. He was last seen on Jan. 24, 1947. His blood pressure was 116 systolic and 80 diastolic. Vision was 20/50 in the right eye and 20/25 in the left eye, unimproved. Examination of the interior showed that the papilledema had subsided. The exudate in the right eye was greatly reduced, although there were remnants of the star figure and the macula was still involved. The disks were of fair color, although slightly pale. In the left eye there was scattered exudate, which was rather white and powdery between the disk and the macula. The arteries were entirely normal. There was no denting of the veins. The field in the right eye was normal at the periphery, and the blindspot was not enlarged. A small, wedge-shaped defect remained, however, in the inferonasal quadrant of the right visual field.

SUMMARY AND CONCLUSIONS

The literature on pheochromocytoma of the adrenal gland is reviewed with special reference to pathologic changes in the eye. The dominant finding in cases of this tumor is vascular hypertension, in the course of

which pathologic changes may be found in the retina or in its blood vessels or in both. The findings cannot be differentiated ophthalmologically from those encountered with hypertensive vascular disease ("essential hypertension"). Because the ocular symptoms may be the first, or indeed the only, sign of the disease, the ophthalmologist will often be seen before the internist; and, regardless of the time of its appearance, the onset of failing vision will sooner or later bring him into consultation. The possibility of pheochromocytoma should be considered whenever he finds evidence of vascular disease.

Three cases in children, all with pathologic changes in the retina, are reported.

Dr. George F. Cahill, Dr. Howard H. Mason and Dr. Raynold C. Berke permitted me to report these cases.

PROPTOSIS DUE TO NEUROBLASTOMA OF THE ADRENAL CORTEX (HUTCHINSON'S SYNDROME)

Report of a Case

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NEUROBLASTOMA of the adrenal gland with its subsequent metastases is a serious disease which occurs almost entirely in children. It is of great interest to ophthalmologists because of its metastasis to the orbit, with resultant proptosis, discoloration of the lids and loss of vision; its rarity; its rapidly fatal termination, and its insidiousness and concealment of the primary lesion, causing difficulty in diagnosis in the early stages. The orbit is invariably involved in the metastases, and frequently it is the eye which gives the first noticeable indication of the disease.

Less than 4 cases a year have been recorded since Vinchow [1] discovered his case in 1864, the total number reported up to the end of 1940 being only 291.

The clinical course in cases of this disease is almost universally rapid, progressing to fatal termination. The average duration of the symptoms and signs is two to five months. The average age of patients with the Pepper type, which metastasizes to the mesenteric nodes and the liver, is 6 months, and that for the Hutchinson type, three years and 10 months. It is noteworthy that with the Pepper type the duration is shorter and the age of the patient less than with the Hutchinson type.

The concealment of the primary tumor until its discovery at autopsy is an important feature. The orbital edema and the proptosis are usually the only symptoms noticed at first. As a rule, no abdominal tumor can be palpated early in the disease; of 10 cases described in Hutchinson's original article,[2] an abdominal tumor was palpated in only 5. In most of the cases the first diagnosis is made late in the illness, when metastases are pronounced.

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1. Virchow, R. L.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863-1867, vol. 2, p. 150.

2. Hutchinson, R.: Suprarenal Sarcoma in Children with Metastases in the Skull, Quart. J. Med. **1**:33, 1907.

REPORT OF CASE

History.—H. C., a white boy 15 months of age, was admitted to the hospital on Aug. 22, 1944. According to the mother, the child was apparently normal until July 1944, when he had fever which was ascribed to a streptococcic infection of the throat and which lasted one week. At this time the mother noticed that the left eye was more prominent than the right.

The family and past histories were essentially noncontributory.

Examination.—Physical examination revealed a mass in the upper left quadrant of the abdomen; enlarged glands at each angle of the jaw; an enlarged, rubbery parotid gland on the right side, and pronounced proptosis of the left eye.

The blood count showed a hemoglobin concentration of 56 per cent but otherwise nothing abnormal. The urine was essentially normal.

Fig. 1.—Characteristic proptosis and edema in a case of Hutchinson's syndrome.

Roentgenologic Report.—Skull and Face: There was a good deal of swelling of soft tissues in the region of the left orbit. Destruction of portions of the facial bones had occurred on the left side, extending posteriorly to involve the ethmoid and sphenoid bones and portions of the frontal bone. These destructive processes were the result of a tumor growing in this region, which was thought to be a neuroblastoma.

Long Bones: Radiolucent areas were present in the upper ends of the humerus and femur on each side, indicating that the destructive processes in the bone were metastatic.

Diagnosis.—The provisional anatomic diagnosis was neuroblastoma of the left adrenal gland, with invasion of the left renal pelvis; metastases to the retroperitoneal lymph nodes, the liver, the cervical lymph nodes, the right side of the mandible and the left orbit (with extensive destruction), causing extreme proptosis, and compression of the right frontal lobe by a large metastatic lesion in the skull.

Course of Illness.—On the patient's admission to the hospital, it was the consensus that the disease was Hutchinson's syndrome. On consultation, I was advised that treatment would be of no avail. The course of the patient's condition was progressively downhill; the proptosis increased, and the patient gradually became more lethargic. Death occurred forty days after his admission.

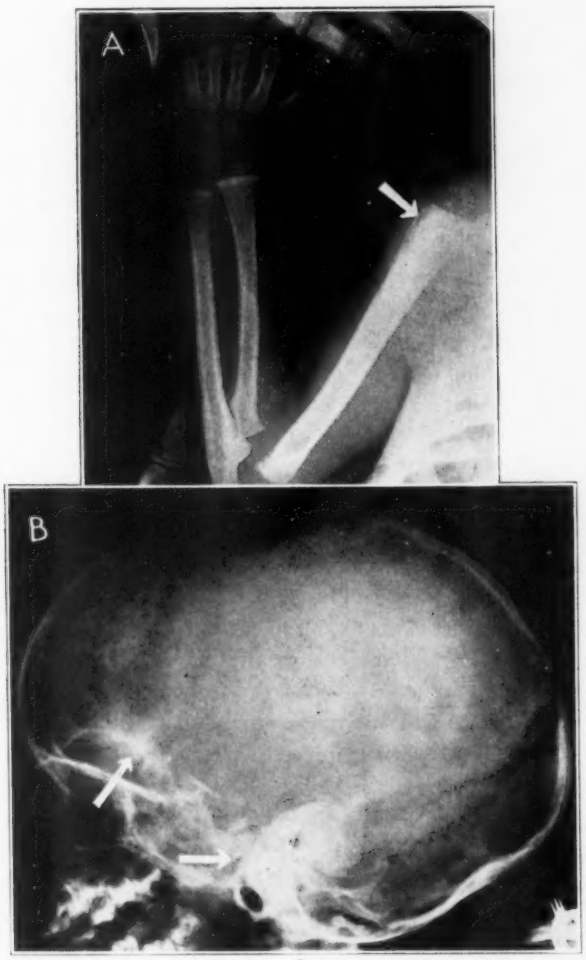

Fig. 2.—*A*, radiolucent areas in the humerus; *B*, destructive processes in the skull, resulting from metastases from the neuroblastoma (arrows).

Report of Autopsy.—Autopsy revealed neuroblastoma of the left adrenal gland, with invasion of the left renal pelvis; metastases to the retroperitoneal lymph nodes, the right side of the mandible and the left orbit (with extensive destruction), causing extreme proptosis of the eye, and compression of the right frontal lobe by a large metastatic lesion of the skull.

COMMENT

Malignant tumors in the region of the adrenal glands are not uncommon in children. The majority of such tumors are composed of embryonically young cells, derived from the sympathetic nervous system, which metastasize so readily that the outcome is almost invariably fatal. To these neoplasms the terms neurocytoma, neuroblastoma, sympathogonioma and sympathicoblastoma have been applied. Less common is the ganglioneuroma, a tumor of similar origin but not highly differentiated.

Virchow [1] is credited with being the first to recognize the nature of these tumors of the adrenal cortex in children. Prior to his work the neoplasm was not considered to be of nervous origin but was thought to be a round cell sarcoma of the adrenal gland. Virchow referred to the tumor as a glioma. To Hutchinson,[2] in 1907, and Pepper,[3] in 1910, goes the credit of effectively describing the clinical picture of this disease. Wright and Page [4] were the first to use the term neuroblastoma. In 1910 they established the theory of the neuroblastic origin of this tumor. Kato and Wachter [5] recently reviewed a fairly large number of the reported cases in order to determine whether the tumor was a neuroblastoma. In some cases the clinical diagnosis seemed correct but the histologic features were incompatible with those of a true neuroblastoma.

The various types of tumors arising from the adrenal gland may be traceable to the development of that gland. The adrenal cortex is derived from the mesoderm of the wolffian ridge, but the adrenal medulla has an entirely different origin—the ectoderm of the primitive neural crest. The neural crest gives rise to two types of cells: the stationary cells, which develop into the cells of the dorsal root ganglions, and the migrating cells, from which the sympathetic ganglion cytons and the chromaffiin cells of the adrenal medulla are derived. The undifferentiated migratory cells are sympathetic neuroblasts. Tumors composed of undifferentiated neural cells are usually neuroblastomas and are highly malignant. Tumors made up of differentiated cells are benign and may be composed of mature nerve cells and fibers (ganglioneuroma), of chromaffin cells (paraganglioma) or of elements of chromaffin cell structure (pheochromocytoma).

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3. Pepper, W. A.: Study of Congenital Sarcoma of the Liver and Suprarenal, Am. J. M. Sc. **121**:287, 1901.

4. Wright, F. H., and Page, B. H.: Neurogenic Tumors of the Sympathetic Nervous System in Children: A Report of Three Cases Surviving a Year or Longer, J Pediat. **14**:137, 1939.

5. Kato, K., and Wachter, H. E.: Adrenal Sympathetic Blastoma in Children, J. Pediat. **12**:449, 1938.

Metastases are widespread. In the Pepper type the mesenteric lymph nodes and the liver are predominantly involved; in the Hutchinson type the skull and the periorbital area are particularly affected. Originally, the tumor may resemble the ganglioneuroma, and the metastases have a typical neuroblastomatous formation.

Clinically, anemia is a striking factor in all cases, the changes in the blood being thought of representing as a profound secondary anemia. Leukocytosis was not recorded in any case. An abdominal tumor in either loin was found in only half the cases. In two thirds of the cases proptosis or discoloration of the eyelids on one or both sides was reported. The progress of the disease was rapid in every instance; the younger the child, the more rapid the course appeared to have been. The duration of life from the time the earliest signs were observed was about six months for the oldest child and only one month for the youngest. The advance of the growth is characterized by progressive exhaustion and anemia and by indications of increased intracranial pressure, such as torpor, intense optic neuritis and baldness. The primary growth may be overlooked; in some cases it could not be detected even though the regions were especially examined for it by palpation.

Fesenmaier [6] stated that in some cases pain in the abdomen, leading to the discovery of a palpable mass, may be the initial symptom, or, more commonly, swelling of the eyelids and protrusion of the eyes may attract the attention of the parents. Protrusion of one or both eyeball may be so extreme as to cause necrosis.

Microscopic Pathology.—Smears made by Kato and Wachter from materials aspirated from both the marrow of the sternum and a cervical lymph node contained clusters of typical slightly basophilic cells, with relatively large hyperchromatic nuclei and fluid-like cytoplasm, which was usually scant.

Such cells, when later associated with the malignant cells similarly demonstrated in the tumor, were identified as metastatic sympathicoblasts or neuroblasts from the primary focus in the adrenal glands. Similar cells and groups of cells, often with two or three nuclei and of larger dimensions, were also observed in the imprint preparations made from the cut surface of the metastatic nodule in the skull.

No typical rosette formation of the pathologic cells was seen in any of the preparations studied; instead, there were seen the bonelike aggregations of cells described more typically as mosaic patterns.

For this reason, the general configuration of cell clusters characterizing this type of neoplasm should be referred to as "pseudorosettes," or, preferably, "mosaics."

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6. Fesenmaier, O. B.: Sympathetic Neuroblastoma, Minnesota Med. **23**:244, 1940.

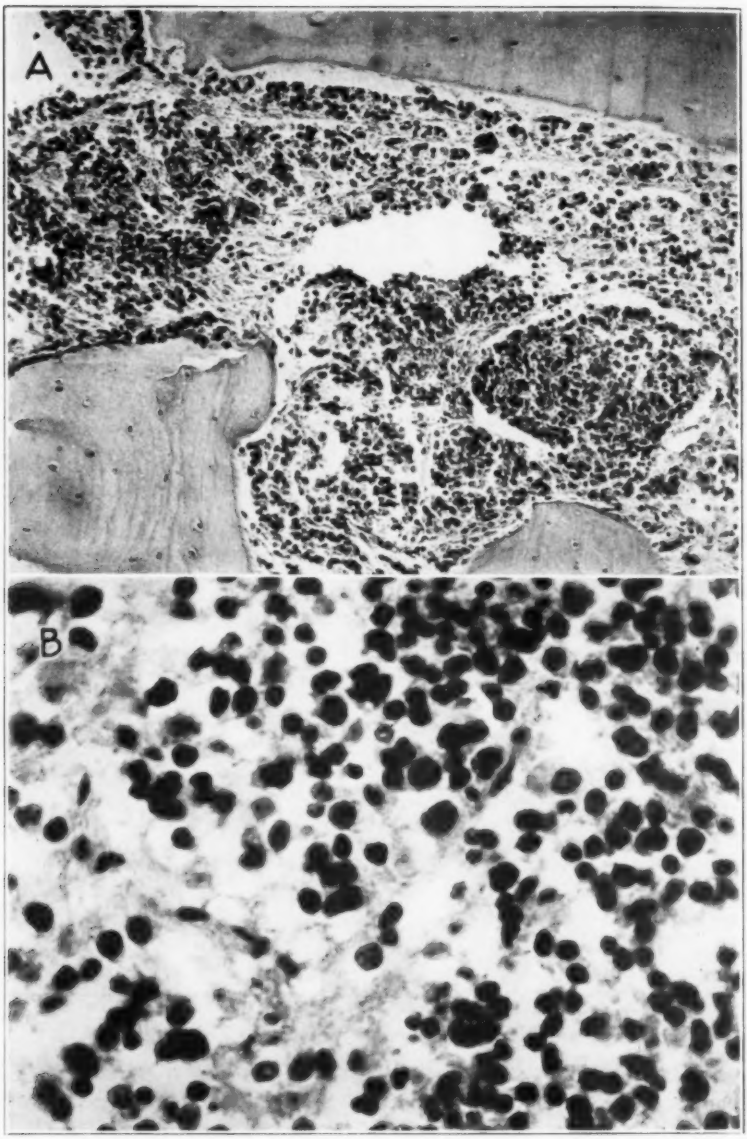

Fig. 3.—*A*, microscopic appearance of cells of a neuroblastoma invading normal tissue; *B*, magnification of the tumor cells shown in *A*.

Diagnosis.—The diagnosis is based on (1) the age of patient, (2) the blood picture, (3) the presence of a palpable mass in the abdomen and (4) the observation of proptosis with orbital metastases.

DIFFERENTIAL DIAGNOSIS

The clinical characteristics of tumor of the adrenal cortex are hirsutism, pubertas precox and, frequently, an increasing blood pressure. Wilms's tumor usually occurs in children over 2 years of age and responds to irradiation. The tumor is frequently palpable. A pyelogram usually aids in the diagnosis. Hematuria occurs sooner or later. Involvement of the bone is rare, but when present the pelvis is the most likely site. Ascites is more likely to occur with lymphosarcoma than with other types. The superficial lymph nodes are often involved. They can be removed for biopsy. The malignant growth responds well to irradiation. Ovarian tumors are rare in children. The large tumors are frequently movable; they grow out of the pelvis. Bimanual examination is of diagnostic aid. In cases of tumors which are twisted on the pedicle, the picture is that of an acute abdominal condition with leukocytosis. In cases of leukemia, the general picture resembles that of a neuroblastoma of the adrenal gland. Repeated studies of the blood and bone marrow punctures should ultimately confirm the diagnosis. The patient with chloroma is usually older. The associated clinical features are those of leukemia. It must be borne in mind that the osseous changes of lymphatic leukemia may resemble greatly those of neuroblastoma of the adrenal cortex. The child with Hand-Schüller-Christian disease is usually older. The splenic enlargement is more pronounced. Studies of the blood lipids should be helpful. Roentgenologic study shows large circular defects in the skull. Ewing's sarcoma occurs late in childhood. Roentgenograms show an onion arrangement of the layers in the periosteal reaction. Occasionally the possibility of rheumatic fever must be eliminated. However, this should be done with ease when the entire picture is considered. Probably the greatest difficulty occurs in differentiation of neuroblastoma of the adrenal gland from lymphosarcoma, acute leukemia and chloroleukemia.

TREATMENT

Treatment up to this time has proved almost entirely ineffective. Irradiation produces a slight temporary response, while surgical intervention is usually followed by death within a short period. It must be mentioned, however, that a case was reported by Lehman [7] in which operation was performed in 1916 and the patient was still living and well in 1931, fifteen years later.

7. Lehman, E. P.: Adrenal Neuroblastoma in Infancy—Fifteen Year Survival, Ann. Surg. **95**:473, 1932.

SUMMARY

1. Proptosis of one or both eyes due to neuroblastoma of the adrenal cortex is seen almost entirely in very young infants, especially boys.

2. This condition is highly malignant, and death occurs usually within three months after appearance of the first sign.

3. The prognosis is bad; and up to the present treatment has been of no avail.

4. Neuroblastoma of the adrenal cortex must always be considered in the cases of young male children when pain in the bone, bulging of the eyeball and an abdominal mass are present.

Dr. A. C. Snell Jr., of Rochester, N. Y.; Dr. C. E. Iliff, of Baltimore, and Dr. Paul Van Natta, of Washington, D. C., assisted in the preparation of this paper.

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INFECTION OF THE HUMAN EYE WITH CRYPTOCOCCUS NEOFORMANS (TORULA HISTOLYTICA; CRYPTOCOCCUS HOMINIS)

A Clinical and Experimental Study with a New Diagnostic Method

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MARIAN C. SHEVKY, A.B.
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SINCE slightly more than 100 cases of infection with Cryptococcus neoformans (Torula histolytica; Cryptococcus hominis) have been reported in the literature up to the present time, the disease should no longer be considered rare. The clinical, histopathologic and mycologic features have been adequately reviewed by Stoddard and Cutler,[1] Freeman,[2] Binford,[3] Dodge,[4] Benham[5] and Cox and Tolhurst.[6] Although a variety of ocular complications, including photophobia, diplopia, ptosis, rigidity of the pupils, amblyopia, strabismus, aniseikonia, nystagmus, neuroretinitis, papilledema, retinal hemorrhages, primary optic nerve atrophy and ophthalmoplegia, have been observed with a

This study was aided by a grant from the Columbia Foundation of California.

A preliminary report on this study appeared in Federation Proceedings (**4**:151, 1945).

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1. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

2. (*a*) Freeman, W.: Torula Infection of the Nervous System, Jahrb. f. Psychol. u. Neurol. **43**:236, 1931. (*b*) Freeman, W., and Weidman, F. D.: Cystic Blastomycosis of the Cerebral Gray Matter, Caused by Torula Histolytica, Stoddard and Cutler, Arch. Neurol. & Psychiat. **9**:589 (May) 1923. (*c*) Freeman, W.: Torula Meningo-Encephalitis, Tr. Am. Neurol. A. **56**:203, 1930.

3. Binford, C. H.: Torulosis of the Central Nervous System, Am. J. Clin. Path. **11**:242, 1941.

4. Dodge, C. W.: Medical Mycology: Fungous Diseases of Men and Other Mammals, St. Louis, C. V. Mosby Company, 1935, p. 333.

5. Benham, R. W.: Cryptococci: Their Identification by Morphology and by Serology, J. Infect. Dis. **57**:255, 1935.

6. Cox, L. B., and Tolhurst, J. C.: Human Torulosis: A Clinical, Pathological and Microbiological Study with a Report of Thirteen Cases, Melbourne, Melbourne University Press, 1946.

fair degree of regularity in this disease (Bettin [7]; Freeman [2a]; Holt [8]; Marshall and Teed [9]; Watts [10]; Reeves, Butt and Hammack [11]; Wade and Stevenson,[12] and others), few ophthalmologists have had the opportunity to make the diagnosis [13]; and only one communication dealing with an orbital infection due to C. neoformans has appeared in the literature.[14]

We present the following interesting history of a patient whose initial symptoms related to poor vision and who immediately consulted three ophthalmologists in succession. The diagnosis, however, was not suspected, even after one eye had become blind and was enucleated. A culture of C. neoformans which we isolated from the remaining eye during the life of the patient was injected into the anterior chamber of rabbit eyes, and this procedure led to the development of a new diagnostic test. The case also afforded the opportunity to observe, for the first time, the early histopathologic changes which occur in this disease.

REPORT OF A CASE

P. A., an Italian aged 56, consulted an ophthalmologist in July 1943 because of failing vision in the right eye. He was referred to another ophthalmologist, who made the diagnosis of a "cystic growth" in this eye. In August 1943 enucleation was performed by the first ophthalmologist; unfortunately, the contents of the eyeball were discarded, and only the choroid and cornea were sectioned.

The pathologic report reads as follows: "The specimen submitted is an eye which had previously been sectioned and the contents of both chambers evacuated. The globe was collapsed, and it had been fixed in dilute solution of formaldehyde U. S. P. in this state. Macroscopic examination failed to reveal any abnormalities. Microscopic examination showed areas of infiltration with small groups of lymphocytes and plasma cells, but no evidence of tumor. The diagnosis was that of an inflammatory process."

In the light of subsequent observations, fragments of tissue from the right eye were carefully reexamined, but no evidence of cryptococci was apparent. Our

7. Bettin, M. E.: Report of a Case of Torula Infection, California & West. Med. **22**:98, 1924.

8. Holt, R. A.: The Identification of Blastomycoides Histolytica in Three Infections of the Nervous System, J. Lab. & Clin. Med. **27**:58, 1941.

9. Marshall, M., and Teed, R. W.: Torula Histolytica Meningoencephalitis, J. A. M. A. **120**:527 (Oct. 17) 1942.

10. Watts, J. W.: Torula Infection, Am. J. Path. **8**:167, 1932.

11. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System: Report of Six Cases with Three Autopsies, Arch. Int. Med. **68**:57 (July) 1941.

12. Wade, L. J., and Stevenson, L. D.: Torula Infection, Yale J. Biol. & Med. **13**:467, 1940-1941.

13. Cohen, M.: Binocular Papilledema in a Case of Torulosis Associated with Hodgkin's Disease, Arch. Ophth. **32**:477 (Dec.) 1944.

14. Gill, W. D.: Torula Mycosis in Man with Special Reference to Involvement of the Upper Respiratory Tract, with Case Report, Tr. Am. Laryng., Rhin. & Otol. Soc. **40**:247, 1934.

report was as follows: There were two defects in the sclera, which were lined with material undergoing coagulation necrosis. One defect penetrated the sclera; the other did not. They appeared to be at the site of cauterization. The cornea showed an old ulceration, the epithelium at the edge of the ulcer being hyperplastic and forming a rounded margin. Sections containing retina showed it to be the site of a chronic inflammatory process, as manifested by the presence of lymphocytes and macrophages. Some of the macrophages contained melanotic pigment. At the ora serrata the choroidal pigment had migrated into the sclera. The choroid was thickened and contained lymphocytes.

After enucleation, the patient returned to work but was unable to continue with his usual activities because a defect had developed in the field of vision of the remaining eye. Shortly thereafter he had a mental upset and was taken to a sanatorium, where he stayed from October 15 to November 7. His mental condition improved, but the vision in his left eye became progressively worse, until, in November 1943, he could merely count fingers at 10 inches (30 cm.).

Past History.—The patient had been in an automobile accident two years previously but gave no history of fracture or of unconsciousness. About ten years prior to hospitalization he noticed a swelling on the dorsum of his hand close to his thumb; this did not increase in size and was not painful.

Physical Examination.—The patient was well developed and well nourished. He was in bed and responded sluggishly to questioning. The head was of normal contour. The right eye was replaced by a prosthesis; the pupil of the left eye was fixed. The conjunctiva was slightly injected. Multiple fine deposits were present on the posterior surface of the cornea; aqueous floaters were graded 4 plus; fine deposits were noted on the anterior capsule of the lens. Vitreous floaters, grade 4 plus, were present. A large retinal detachment extended from 6 to 11 o'clock; it was not wavy and did not fluctuate but had the appearance of a cystic mass. Transillumination was even and revealed nothing abnormal. Hearing was essentially normal.

The lungs appeared clear on percussion and auscultation. The heart sounds were of good quality; the rhythm was regular; there were no murmurs. The blood pressure was 128 systolic and 80 diastolic. The abdomen was not remarkable. The extremities were normal except for a mass over the dorsum of the right hand close to the thumb; this tumor was freely movable, about the size of a peach and of moderate consistency. The neurologic status was essentially normal. The mental state was not studied.

Diagnosis.—The right eye was replaced by a prosthesis. The left eye presented a retinal detachment, possible cyst of the retina and uveitis; a lipoma was present on the dorsum of the right hand.

Operation and Subsequent Course.—On November 23 a trephine opening was made in the sclera (but not in the choroid) 12 mm. from the limbus and inferior to the medial rectus muscle. A heavy, viscid, brownish fluid drained through the opening. The fluid was cultured, and a pure growth of C. neoformans (T. histolytica; C. hominis) was obtained. On December 3 a second trephination of the sclera was performed about 12 mm. from the limbus at 7 o'clock. An 18 gage needle was inserted into the subretinal space, and about 1 cc. of a heavy, viscid, gelatinous fluid and 2 cc. of a yellowish fluid were aspirated. Cultures of this material revealed a crytococcus similar to that obtained after the first operation.

The family reported that the patient died in 1946. There was no autopsy.

LABORATORY INVESTIGATIONS

The fluid obtained by trephining the sclera was cultured on corn meal agar, blood agar and thioglycollate broth. A pure culture of a yeastlike organism developed, which after inoculation into mice was identified as C. neoformans (T. histolytica or C. homonis), group III (Benham [5]). Subcultures were sent to Dr. Morris Moore, Barnard Free Skin and Cancer Hospital, St. Louis, and to Dr. Rhoda W. Benham, Medical Center, New York, both of whom confirmed our observations.

CULTURAL CHARACTERISTICS

The colonies of cryptococci were creamy white, becoming tan with age; they were fairly moist, nonfriable, finely granular, opaque and umbonate, with an

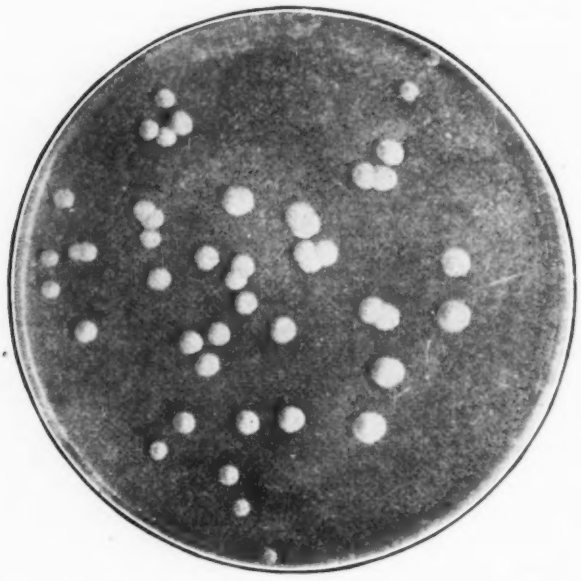

Fig. 1.—Colonies of Cryptococcus neoformans on a corn meal agar plate.

entire periphery (fig. 1). There was no fermentation of dextrose, maltose, levulose, sucrose, lactose, galactose or mannite after one week's observation. Maltose and sucrose showed slight acid formation after four weeks' incubation. There was pellicle formation in milk. No liquefaction of gelatin was seen during three months' observation, and there was no evidence of mycelial formation. Multiplication occurred by budding only. Ascospore formation was not observed.

PATHOGENICITY FOR MICE

Intraperitoneal Route.—Two mice were inoculated intra-abdominally with cultures of cryptococci. One died nineteen days later; the other was moribund and was killed. Cryptococci were recovered in pure culture from the brain and genitalia of both animals. Dr. Morris Moore also inoculated several mice intraperitoneally with our strain. They died four to eight days after injection. The organisms were demonstrable in stained section of various viscera, including the pancreas.

Intravenous Route.—On Dec. 28, 1943, 3 mice were inoculated intravenously with doses of 0.25 cc. of a suspension of a turbidity equal to that of the no. 1 tube of a McFarland nephelometer. Five days later one animal was moving about in circles and had a tumor-like swelling in the occiput. It died forty-one days after injection. Autopsy revealed that the brain was soft and gelatinous. The organism was cultivated from the brain, liver and spleen and from the gelatinous tumor on the occiput, which had eroded through the skull. The second mouse was found dead on the twentieth day, and the third on the forty-first day, after injection. Cryptococci were isolated from the viscera of each animal.

PATHOGENICITY FOR RABBITS

Intraocular Route.—Eight rabbits received injections of cultures into the anterior chamber. The technic was carefully controlled, so as not to injure the iris.[15] Anesthesia was induced by intravenously administered pentobarbital, supplemented by ether in order to prevent the animal from struggling. The dose was 0.1 cc. of a twenty-four hour culture which was made up to a turbidity equal to that of the no. 1 tube of a McFarland nephelometer and was further diluted to 1:100 with buffered saline solution. Only one eye of an animal was inoculated, the second serving as a control. Enucleations for the purpose of histologic study were made at intervals of seventeen and one hundred and twenty days after injection.

Animals Killed for Observation After Seventeen Days: The results with 4 rabbits were essentially similar, and the protocol of only 1 will be cited.

Rabbit 677: Injection into the left eye was made on Dec. 28, 1943. No noteworthy symptoms appeared until six days later, when there was severe inflammation of the upper palpebral conjunctiva and the entire bulbar conjunctiva, with moderate iritis. The cornea was clear. Four days later there was severe congestion of the sclera and lids and two tiny opaque spots were seen in the center of the pupillary area. The cornea had a faint, milky opacity. Seventeen days after injection the lids were red and showed a slight discharge. The vessels of the sclera were congested; the cornea had a milky opacity, and it was difficult to see the markings of the iris. The eye was now enucleated for study.

Histopathologic report: A slight exudate of polymorphonuclear leukocytes and some monocytes was observed along the periphery of the cornea, with a minute area of acute necrosis. Along the anterior surface of the iris and the posterior surface of the cornea there was a delicate festoon of rosettes (fig. 2), in the center of which was a crytococcus (torula). Surrounding the organism was a single row of cells composed of both polymorphonuclear leukocytes and monocytes. Where the rosette was detached and lay free in the anterior chamber, the single row of host cells surrounding the organism was conspicuous and suggested that the cells adhered to the gelatinous capsule. The reaction was greatest at that part of the anterior chamber which was opposite the point of inoculation. Here the monocytes had evolved into macrophages and in a few instances had two to three nuclei. Occasionally an engulfed organism was seen inside a macrophage. The cryptococci were from 5 to 10 microns in diameter, possessed a thick, mucoid capsule, were

15. Benjamin, L., Jr.; Belt, E., and Krichevsky, B.: Total Prostatectomy in the Rabbit and Intra-Ocular Transplantation of Prostatic Tissue, J. Urol. **44**:109, 1940. Gilbert, W., and Plaut, F.: Ueber Kammerwasseruntersuchung: I., Arch. f. Augenh. **90**:1, 1921.

sometimes apiculate and showed definite budding (fig. 3). The organisms and their buds were sometimes a clear, pale green and at other times contained a coarse, dark brown pigment. The iris and ciliary body were edematous (fig. 4). There was no evidence of penetration of the cryptococci into the tissues, although the stroma of the ciliary body was loose and vascular. The posterior chamber was normal.

Animals Killed for Observation After Four Months: The results for the 2 animals in this series were similar.

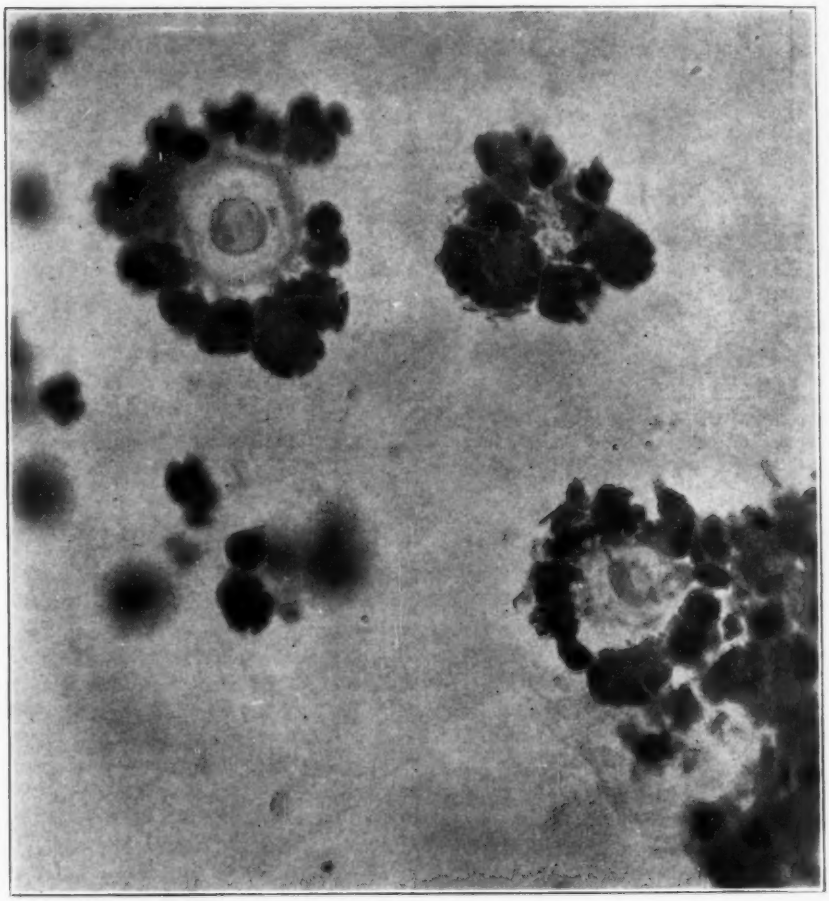

Fig. 2.—Section of rabbit eye (rabbit 676) enucleated one week after injection of cryptococci into the anterior chamber, showing rosette formation.

Rabbit 675: Inoculation was made on December 16.

Twelfth day: Inflammation of the palpebral and bulbar conjunctivas, mild iritis and slight cloudiness of the cornea were noted.

Eighteenth day: The eye was closed; a thick, mucopurulent exudate was seen in the inner canthus; the eyelids were red and sticky; the cornea was slightly opaque, and the bulbar and palpebral conjunctivas were congested.

Twentieth day: The upper palpebral conjunctiva was slightly congested; the lids were normal; the bulbar conjunctiva was slightly congested; a hypopyon extended from 5 to 7:30 o'clock; the cornea was slightly opaque; the iris was nearly normal.

Twenty-seventh day: The palpebral and bulbar conjunctivas were congested; there was a mucopurulent discharge; the cornea had a milky opacity; the iris was difficult to see; the hypopyon was still present; exophthalmos was present.

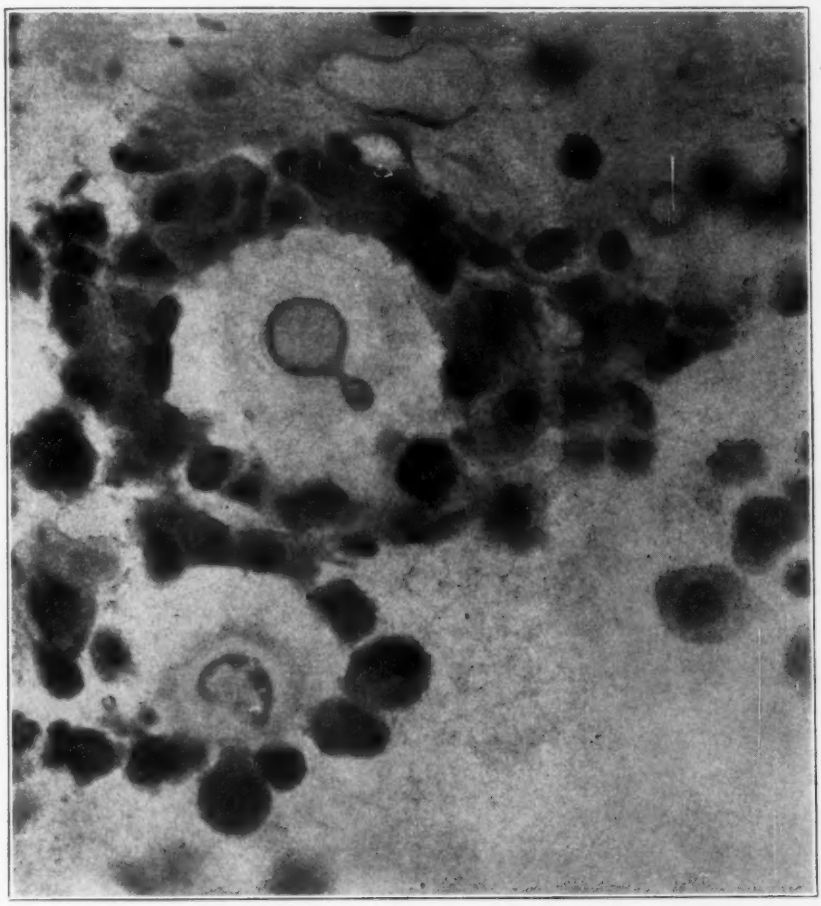

Fig. 3.—Budding organisms, showing mucoid capsule, surrounded by leukocytes and macrophages, and rosette formation (from the same section as that illustrated in figure 2).

Forty-first day: The rabbit appeared groggy and was very quiet in the cage; the eye was held shut; the conjunctiva was congested and glassy; there was no discharge; the iris was obliterated by an opaque cornea; a hypopyon was present; the pupillary area was opaque.

Forty-eighth day: A heavy, narrow, creamy band lay apparently on the posterior surface of the cornea and extended toward the iris; a half-moon-shaped

opacity appeared like a dense, half-ringed synechia at the margin of the iris and adhered to the capsule of the lens; the pupil was small and fixed; the fundus could not be seen; many superficial vessels invaded the cornea at the limbus; the iris was hyperemic.

Fifty-second day: Observation with the slit lamp (Dr. Frank H. Rodin) revealed dense vascularization of the cornea, beginning at the limbus and occupying the whole cornea except for the central pupillary area; a synechia was present at the point where the iris adhered to the lens.

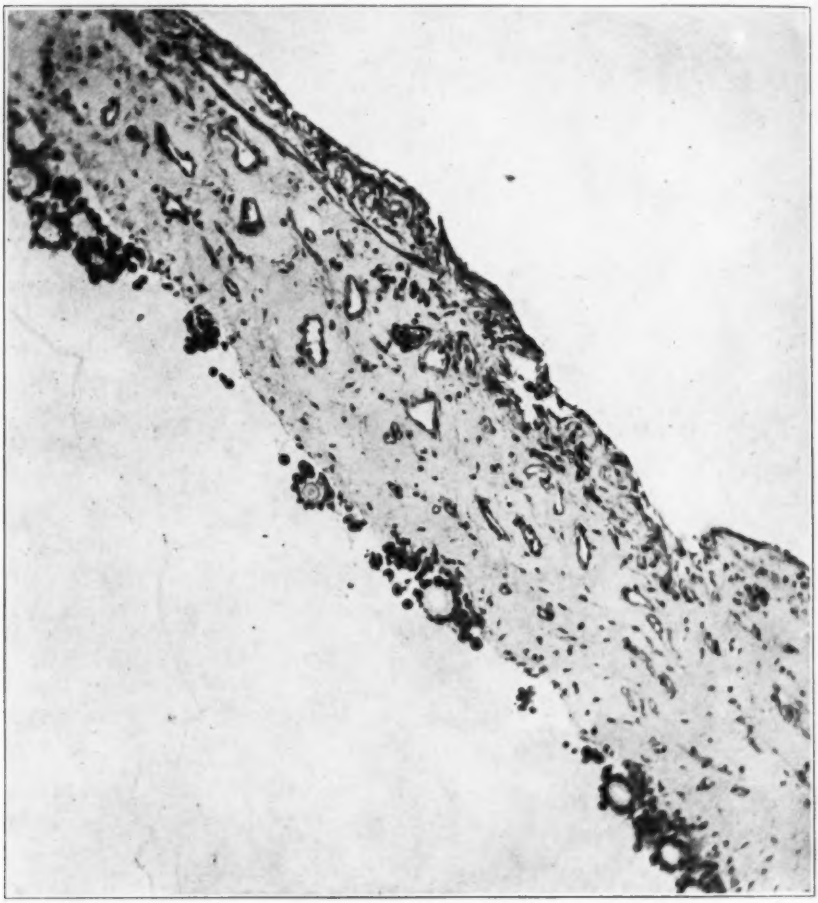

Fig. 4.—Low power magnification of the iris, showing that the cryptococci have not penetrated into tissues of the iris; rosette formation.

Gross pathologic appearance after enucleation (one hundred and twentieth day): The inferior part of the anterior chamber was opaque and creamy, with somewhat nodular conformation. There were small, vesicular blebs over the inferior part of the cornea and the sclera. It was not determined whether these lesions were cysts or emphysematous blebs. A pannus was present over the entire circumference of the cornea but was densest in the inferior part. In vivo the pannus was most intense in the superior part of the cornea. The cornea was opaque, and the pupil was not all distinguishable.

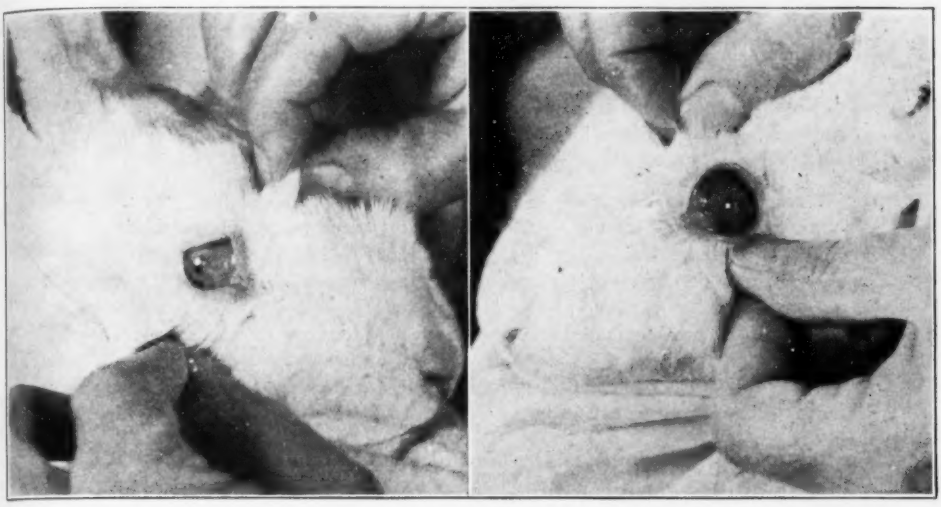

Fig. 5.—Contrasting appearance of the normal (left) and the inoculated (right) eye of a rabbit twelve days after intraocular injection with cryptococci.

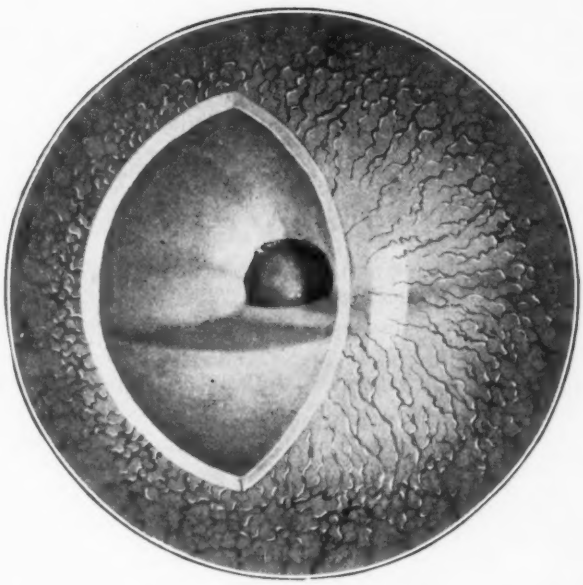

Fig 6.—Appearance of a rabbit eye three weeks after injection into the anterior chamber of Cryptococcus neoformans.

Histologic report: Left eye: The iris was adherent to the cornea, which was scarred and vascularized. In the anterior chamber a dense neutrophilic exudate surrounded the calcifying cryptococci. Another focus contained rings with a few shells of organisms. In the center of a circumscribed abscess were many neutrophils, with an outer ring of macrophages and lymphocytes. The macrophages were large and had ingested much detritus. A few abortive giant cells were seen.

Right eye: The eye was normal.

Other Routes of Infection.—Three other routes of inoculation were used in rabbits, with negative results. When injections were made subconjunctivally or intradermally, there was only a local bleb or a small nodule with slight inflammation, which persisted for several days. Intravenous injection of 3.0 cc. into 2 rabbits elicited no symptoms during a period of observation of four and one-half months. These animals looked well when killed and showed no evidence of infection.

COMMENT

The present case of infection of the eye with C. neoformans (T. histolytica; C. hominis) is the second such instance on record. Other communications dealing with localized lesions due to this organism have been published. Among the sites of infection are the knee,[16] nasopharynx,[17] pelvis,[18] spine,[19] skin[20] and rectum.[21] It is likely that all cases of such lesions represent localized manifestations of systematic mycoses.

It was not possible to establish the portal of entry in our case. Some authors have suggested the respiratory tract. It must be pointed out, however, that Fazakas[22] found cryptococci repeatedly in both the normal and the diseased conjunctiva, and this surface might have served as the avenue of infection. Since the identification of C. neoformans depends largely on the demonstration of its pathogenicity, the choice of a suitable susceptible animal becomes a matter of considerable importance. There has been much discussion of this subject in the literature.

16. Kessel, J. F., and Hoetzwart, F.: Experimental Studies with Torula from a Knee Infection, Am. J. Trop. Med. **15**:467, 1935.

17. Jones, E. L.: Torula Infection of the Nasopharynx, South. M. J. **20**:120, 1927.

18. McGehee, J. L., and Michelson, I. D.: Torula Infection in Man, Surg., Gynec. & Obst. **42**:803, 1926; cited by Jones.[17]

19. Brewer, G. E., and Wood, F. C.: Blastomycosis of the Spine, Ann. Surg. **48**:889, 1908; cited by Reeves, Butt and Hammack.[11]

20. Mook, H. W., and Moore, M.: Cutaneous Torulosis, Arch. Dermat. & Syph. **33**:951 (June) 1936. Wile, U. J.: Cutaneous Torulosis, ibid. **31**:58 (Jan.) 1935.

21. Allen, V. K., and Lowbeer, L.: Rectal Ulcers with Perirectal Fistula as Port of Entrance for Torula Encephalitis, South. M. J. **38**:565, 1945.

22. Fazakas, A.: Ueber die Schimmelpilze des gesunden und kranken Auges, Arch. f. Ophth. **138**:416, 1938.

As pointed out by Gray,[23] Kessel,[16] Longmire and Goodwin,[24] Crone, DeGroat and Wahlin[25] and Freeman,[2] rabbits, when infected, show irregular results or are entirely resistant. By injecting the organisms into the anterior chamber of these animals, we produced severe keratitis, iritis, pannus and total blindness. The use of the intraocular route has the advantage that the lesion can be seen grossly within a week after infection and reaches its full development at the end of fourteen to seventeen days.

The histologic features of these early lesions are characteristic and differ from those seen late either in the experimental or in the natural disease. Thus, along the anterior surface of the iris and the posterior surface of the cornea we observed a delicate festoon of rosettes, in the center of which was a cryptococcus. Surrounding the organism was a single row of cells, composed of both polymorphonuclear leukocytes and monocytes. This rosette formation has not previously been described. The only observation in the literature which resembles it is that of Rappaport and Kaplan,[26] who, when referring to a metastatic cutaneous lesion due to the torula, stated:

> Under the intact skin at one margin of the ulcer there was a marked, diffuse infiltration of the yeastlike organisms in a granular débris. Some round cells and many fibroblasts were present. The latter in some places revealed a peculiar arrangement, three to four of the cells surrounding one organism about which there was a clear space, giving the appearance of an organism within a capillary. [no illustrations]

The reaction previously described as a rosette formation is interpreted as due to the opportunity to observe advantageously the exudative response of the tissues to cryptococci in the initially acellular space of the anterior chamber of the eye and in the early stage of infection. The conventional description of the late stages of torulosis is that of a chronic granuloma with caseous areas resembling tuberculosis. The characteristic features include the formation of giant cells and the absence of polymorphonuclear leukocytes. This picture may be explained on the basis of the advanced age of the lesions. Thus, Stoddard and Cutler[1] described the lesion in the liver of a rabbit autopsied three weeks after intraperitoneal inoculation:

> . . . a large area . . . with central caseation, surrounded by epithelioid cells, then a zone of thick infiltration with lymphoid cells, containing many eosino-

23. Gray, F. C.: Two Cases of Torula Meningitis, with Special Reference to Laboratory Findings, South African M. J. **14**:65, 1940.

24. Longmire, W. P., Jr., and Goodwin, T. C.: Generalized Torula Infection, Bull. Johns Hopkins Hosp. **64**:22, 1939.

25. Crone, J. T.; DeGroat, A. F., and Wahlin, J. G.: Torula Infection, Am. J. Path. **13**:863, 1937.

26. Rappaport, B. Z., and Kaplan, B.: Generalized Torula Mycosis, Arch. Path. **1**:720 (May) 1926.

philic cells, with a slight surrounding connective tissue band. . . . [In the brain, there occurs] a chronic meningitis in which definite torula organisms are found. The cells consist chiefly of large mononuclear cells and sometimes contain organisms. There are moderate numbers of plasma cells, but no polynuclear cells. The organisms are scarce and show much degeneration. The large phagocystic mononuclear cells are filled with hyaline droplets or vacuoles. The cortex near the lesion has a slight increase in glia tissue, with spider glia cells. In the cortex are focal lesions consisting of accumulations of mononuclear, lymphoid and plasma cells.

These authors concluded that the torula does not attract polymorphonuclear leukocytes at any stage and that its pathogenicity for rabbits is slight.

Freeman[26] described the histopathologic characteristics of human torular meningoencephalitis as follows:

Microscopically, the diffuse meningitis is characterized by marked proliferation of endothelial cells and the formation of new fibrous tissue, together with infiltration by lymphocytes and plasma cells, but practically never by polymorphonuclear leukocytes, and by the occurrence of a moderate number of giant cells, usually with centrally placed nuclei less often of the Langhans type.

In general, as shown by Crone, DeGroat and Wahlin,[25] the degree and character of the inflammatory response to infection with C. neoformans depend on the local supply of cells capable of being mobilized as macrophages in any given organ or tissue. Our data emphasize the importance of considering the age of the lesion.

SUMMARY

A case of infection of the human eye with C. neoformans (T. histolytica; C. hominis) is reported. The clinical diagnosis was "possible cyst of the retina with retinal detachment and uveitis." The sclera was trephined, and material obtained for culture showed the presence of this yeastlike organism.

By injection of the culture into the anterior chamber of rabbit eyes, it was possible to observe pathologic changes as early as the fifth to the seventh day. These lesions were fairly well established by the seventeenth day. The inferior part of the anterior chamber became opaque; there was plastic iritis, and a pannus developed on the surface of the cornea.

Histologically, there was a slight exudate consisting of polymorphonuclear cells and monocytes along the periphery of the cornea. Along the anterior surface of the iris and the posterior surface of the cornea there was a delicate festoon of rosettes. In the center of each rosette there was a cryptococcus, surrounded by a single row of polymorphonuclear cells and monocytes. The organisms were seen to be engulfed inside macrophages. The early stages of infection in the rabbit eye are there-

fore characterized by the formation of rosettes, which suggest actual agglutination on to the mucous capsule of the cryptococcus; the absence of invasion, and the presence of both acute and chronic exudative responses.

Since in most cases of human infection with C. neoformans the diagnosis has been made either post mortem or late in the disease, after several weeks or months of illness, it is hoped that this new method of intraocular injection of rabbits, together with the description of the early histologic reaction, may contribute to an earlier diagnosis of this fatal disease.

The late Dr. Martin I. Green, of Greens' Eye Hospital, San Francisco, furnished the medical history, and Dr. Arthur Haim referred the patient to us for investigation.

Jewish Hospital, Philadelphia (Dr. Weiss).

Departments of Pathology (Dr. Perry) and Bacteriology (Miss Shevky) of University of California Medical School, San Francisco.

CONTROVERSIAL POINTS IN PENICILLIN THERAPY OF OCULAR DISEASES

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NEW YORK

OUTLINE OF STUDY

I. Parenteral use of penicillin
   - A. Passage of penicillin across blood-aqueous barrier
   - B. Penicillin level in ocular and other body fluids after ligation of renal vessels
   - C. Passage of penicillin from blood into aqueous and vitreous in ocular inflammation

II. Surface applications of penicillin
   - A. Solutions and ointments
   - B. Iontophoretic introduction of penicillin
     1. Conductivity of sodium penicillin
     2. Influence of change in hydrogen ion concentration at cathode on activity of penicillin
     3. Factors acting on passage of penicillin through cornea during iontophoresis
        - (*a*) Flow of electric current from cathode
        - (*b*) Changes in hydrogen ion concentration of bathing fluid
        - (*c*) Polarity of terminal
        - (*d*) Tonicity of penicillin solution
     4. Value of high drug levels in aqueous after corneal iontophoresis or similar procedures
     5. Palpebral iontophoresis

III. Local injections of penicillin
   - A. Under conjunctiva
   - B. Into anterior chamber
   - C. Into lens
   - D. Into vitreous
     1. Crystalline penicillin
     2. Penicillin and antitoxin

IV. General conclusions

This study was supported by the Knapp Memorial Foundation.

Presented as a candidate's thesis in partial fulfilment of the requirements for membership in the American Ophthalmological Society, 1947.

From the Department of Ophthalmology of Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

The literature on the use of penicillin in ophthalmology has grown extensively in the last few years and has been summarized in several reviews. It is the purpose of this paper to study certain contradictions in, and unsettled questions concerned with, various types of ocular penicillin therapy rather than to complete the list of pertinent publications.

I. PARENTERAL USE OF PENICILLIN IN OPHTHALMOLOGY

Most investigators agree that parenteral penicillin therapy in ophthalmology should be limited to severe infections of the lids, conjunctiva and orbit. The opinion is based less on clinical observations than on early experimental data which demonstrated that the intraocular fluids of normal human eyes and of normal eyes of experimental animals showed little or no antibacterial activity after systemic use of penicillin in common doses.[1] However, extracts from other parts of the normal eye of rabbits, such as the sclera, conjunctiva and chorioretina, contained more penicillin.[1b, c] Paracentesis [2] and experimentally induced intraocular vasodilatation [3] brought about an increase in the drug level in the aqueous after parenteral injection of penicillin, but even then its height compared unfavorably with that obtained with local procedures. The results of these studies on distribution of penicillin in the normal eye explain the preference for topical methods, since the assumption that better therapeutic effects are obtained with higher drug levels has been applied to penicillin.

A. PASSAGE OF PENICILLIN ACROSS THE NORMAL BLOOD-AQUEOUS BARRIER

The poor penetration of penicillin into the intraocular fluids and ocular tissues from the blood is similar to that reported for cerebrospinal fluid and brain tissue, although the blood-brain barrier seems to interfere with the transport of the drug into the spinal fluid more than the blood-aqueous barrier in the transfer of penicillin into the

1. (*a*) von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth. **31**:1 (Jan.) 1944. (*b*) Struble, G. C., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye, J. A. M. A. **125**:685 (July 8) 1944. (*c*) Bellows, J. G.: Penicillin Therapy in Ocular Infections, Am. J. Ophth. **27**:1206 (Nov.) 1944. (*d*) Leopold, I. H.: Intravitreal Penetration of Penicillin and Penicillin Therapy of Infections of the Vitreous, Arch. Ophth. **33**:211 (March) 1945. (*e*) Rycroft, B. W.: Penicillin and the Control of Deep Intraocular Infection, Brit. J. Ophth. **29**:57 (Feb.) 1945.

2. (*a*) von Sallmann and Meyer.[1a] (*b*) Struble and Bellows.[1b] (*c*) Town, A. E., and Hunt, M. E.: Penicillin in the Aqueous Humor, Am. J. Ophth. **29**:171 (Feb.) 1946.

3. (*a*) Leopold.[1d] (*b*) Mann, I.: Intraocular Use of Penicillin, Brit. J. Ophth. **30**:134 (March) 1946.

ocular fluids. McDermott and Nelson [4] enumerated three mechanisms which might account for the fact that only traces of penicillin are assayable in the spinal fluid after parenteral use of the compound: (1) the binding of penicillin to nondiffusible components of serum; (2) the molecular structure of penicillin, which would make the compound unsuitable for the transport across the blood–spinal fluid barrier, and (3) rapid inactivation of penicillin by some constituent of nerve tissue or cerebrospinal fluid after the drug has passed the barrier. On the basis of dialysis and diffusion experiments, these authors discarded the first mechanism; they could not investigate the second because of the limited knowledge concerning the molecular structure of penicillin at the time of their studies. With regard to the third possibility, it is merely known that cerebrospinal fluid does not inactivate penicillin in vitro.

Thus far, the problem of the transport of penicillin across the blood-aqueous barrier has not been studied. A possible cause of the low penicillin content of the aqueous was revealed in the dialysis experiments of Chow and McKee,[5] which provided evidence that crystalline penicillin combines with human serum albumin; however, this mechanism could be considered a relatively minor factor. Untenable is the theory of inactivation of the antibiotic by ocular fluids or tissues, because penicillin was not destroyed in either aqueous or ground ocular tissues which were stored in the refrigerator for a number of hours. Nor does the gradient of the depletion curve of the aqueous indicate such a loss of potency. Additional evidence was presented by recent experiments of this laboratory in which sodium penicillin in centrifuged vitreous fluid of normal rabbits did not lose its activity more rapidly than a solution of the antibiotic of equal strength in a phosphate buffer when exposed to temperatures of 2, 24 and 37 C. for four hours.

The scarcity of the types of pure penicillin prevented the study of the relation of their stereochemical structure to the transport across the blood-aqueous barrier. The part which the components of this barrier play as possible obstacles to the transfer of penicillin was examined by using cyanide for the in vivo inhibition of the indophenol oxidase (cytochrome oxidase) in the ciliary epithelium.

The work of Warburg [6] on the inhibition of the respiratory mechanism by low concentrations of cyanide was used by Seidel,[7] Schmelzer,[8]

4. McDermott, W., and Nelson, R. A.: Transfer of Penicillin into the Cerebrospinal Fluid Following Parenteral Administration, Am. J. Syph., Gonor. & Ven. Dis. **29**:403 (July) 1945.

5. Chow, B. F., and McKee, C. M.: Interaction Between Crystalline Penicillin and Human Plasma Proteins, Science **101**:67 (Jan. 19) 1945.

6. Warburg, O. H.: Ueber die katalytischen Wirkungen der lebendigen Substanz, Berlin, Julius Springer, 1928.

Friedenwald and Stiehler,[9] Duke-Elder and others [10] as a basis for their various studies on the function of the blood-aqueous barrier. Cyanide solutions were injected into the vitreous (Seidel and Schmelzer), applied by a supravital technic on the excised ciliary body (Friedenwald and Stiehler) or added to the perfusion fluid for use on the isolated dog head (Duke-Elder). None of these experimental approaches was suitable for the current investigation. Pronounced changes in the intraocular pressure due to the injection of any fluid into the vitreous are generally followed by an unpredictable response of the intraocular vessels even when nonirritating solutions are used. Similar objections must be raised in regard to the perfusion experiments, as severe disturbances in the capillary permeability are usually observed in such preparations. The supravital technic of Friedenwald could not be applied, for the concentration of penicillin in the aqueous had to be determined after inhibiting the respiratory mechanism of the ciliary epithelium. A complete or partial suppression of the cyanide-sensitive system in this structure was therefore attempted in vivo with cyanide iontophoresis.

In preliminary experiments, measurements were made of the cyanide concentrations and the protein levels in the aqueous. The effect of the cell poison on the cytochrome oxidase of the ciliary epithelium of albino rabbits was then tested with the indophenol oxidase reaction. In subsequent series of experiments, the amount of penicillin which penetrated from blood to aqueous in the poisoned eyes was compared with that of variously treated control eyes. The inhibition of the cytochrome oxidase in the ciliary epithelium of the eyes treated with cyanide was again verified by the test for indophenol oxidase, and results were collated with those in the control eyes. The influence of the cyanide on the permeability of the intraocular vessels was deduced from the protein content of the aqueous.

Technic of Preliminary Experiments.—For the iontophoretic induction of the cyanide into the anterior segment of the eye, the orifice of the applicator glass tube was widened at the lower end so that its rim fitted the region of the ora serrata. A 0.5 per cent solution of potassium cyanide adjusted to a p_H of 7 with phosphoric acid, or a solution of sodium cyanide of the same strength neutralized with hydro-

7. Seidel, E.: Ueber die Gewebsatmung im Auge und ihre klinische Bedeutung, Ber. d. deutsch. ophth. Gesellsch. **45**:14, 1925.

8. Schmelzer, H.: Mikrochemische Reaktionen am Ziliarepithel, Ber. d. deutsch. ophth. Gesellsch. **45**:259, 1925.

9. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938.

10. Duke-Elder, W. S.; Quilliam, J. C., and Davson, H.: Some Observations on the Present Position of Our Knowledge of the Intraocular Fluid, Brit. J. Ophth. **24**:421 (Sept.) 1940.

chloric acid, was applied iontophoretically at 2 milliamperes for five minutes to the right eye of each rabbit in the series. The left eyes were treated in like manner with a 0.9 per cent solution of sodium chloride or with a phosphate buffer of p_H 7. Other (control) eyes were subjected to histamine iontophoresis. The dihydrochloride salt in a concentration of 0.1 per cent was applied from the anode at 1 milliampere for two minutes. The amount of cyanide in the aqueous was examined at various intervals. Of the three methods of cyanide determination which were tested—the silver nitrate method of Brunswik,[11] the picric acid method of Smith[12] and the bromine method of Aldridge[13]—the last was found suitable for a quantitative spectrophotometric technic.[14]

Two-tenths cubic centimeter of aqueous was diluted with 1 cc. of a 5 per cent solution of trichloroacetic acid and centrifuged. Five-tenths cubic centimeter of bromine water and 0.5 cc. of a 1.5 per cent aqueous solution of sodium arsenate were added to 1 cc. of the supernatant. One cubic centimeter of this solution (A) was mixed with 5 cc. of freshly prepared solution (B), which consisted of 5 cc. of the pyridine reagent (25 cc. of pure redistilled pyridine and 2 cc. of concentrated hydrochloric acid diluted to 100 cc.) and 0.2 cc. of a 2 per cent aqueous solution of benzidine hydrochloride. Ten minutes was allowed for development of color. The results were read against concurrent standards, which gave a straight line in a Coleman spectrophotometer set at a wavelength of 480 microns. One microgram of potassium or sodium cyanide per cubic centimeter could be determined. The protein in the aqueous was determined nephelometrically, as described in a previous article.

Results.—An unneutralized solution of potassium or sodium cyanide (0.5 per cent) caused a diffuse alkali burn of the cornea when it was applied with the ionization method. The cornea later became scarred and vascularized. When the solution was adjusted to a p_H of 7 with phosphoric acid or with hydrochloric acid, a transient haziness of the epithelium and hyperemia of the pericorneal vessels and the vessels of the iris were noted. An average cyanide content of the aqueous of 43.41 micrograms per cubic centimeter was determined thirty minutes after iontophoresis. It decreased to 4.5 micrograms per cubic centimeter in the following hour and a half (table 1). There was no development of color in the samples of aqueous withdrawn three hours after iontophoresis; therefore, the depletion of cyanide from the aqueous is more rapid than that of other compounds (sulfonamide compounds, penicillin).

11. Emich, F.: Microchemical Laboratory Manual, New York, J. Wiley & Sons, Inc., 1932, p. 123.

12. Smith, R. G.: A Method for the Quantitative Determination of Cyanide in Small Amounts, J. Am. Chem. Soc. **51**:1171 (April 5) 1929.

13. Aldridge, W. N.: A New Method for the Estimation of Micro Quantities of Cyanide and Thiocyanate, Analyst **69**:262 (Sept.) 1944.

14. The silver nitrate method was not applicable, since the exposure of samples of normal aqueous to the laboratory air caused the formation of characteristic crystals of silver cyanide. The picric acid method was abandoned because of its unspecificity.

The injurious effect of the neutralized cyanide solution was evidenced not only on the corneal epithelium and the pericorneal and iridal vessels but also on the protein content of the aqueous, which increased considerably. The increase greatly surpassed that observed after iontophoresis with a 0.9 per cent solution of sodium chloride. When a phosphate buffer with a p_H of 7 or the histamine solution was used, the protein values for the aqueous were sometimes in the same range as, but usually lower than, those for the aqueous of the eyes treated with cyanide. The high protein values for the aqueous were taken to indicate increased permeability of intraocular capillaries.

The cyanide which had entered the posterior chamber could not be measured because of the minute amounts of the fluid in this part of the rabbit's eye. Since the quantities of cyanide in the anterior chamber did not signify whether adequate amounts of the compound had entered the ciliary epithelium, it was advisable to apply the indophenol oxidase

TABLE 1.—*Cyanide Content of Aqueous After Iontophoresis with Neutral 0.5 Per Cent Potassium Cyanide*

	Hours After Iontophoresis			
	½	1	2	3
Cyanide concentration, micrograms/cc.	22.50	6.60	3.48	No measurable amount
	44.70	7.20	3.96	No measurable amount
	34.00	16.50-18.80	4.50	No measurable amount
	72.48	14.40	6.10	No measurable amount
Average	43.41	13.50	4.50	No measurable amount

reaction in investigating the inhibition of cyanide and to compare the results with those obtained for control eyes.

Technic of Experiments on Passage of Penicillin Across the Blood-Aqueous Barrier.—Albino rabbits were killed by withdrawing blood from the heart at various intervals after corneal iontophoresis with neutralized cyanide solution (0.5 per cent) for five minutes at 2 milliamperes. The control eyes received the same iontophoretic treatment with a 0.9 per cent solution of sodium chloride or a phosphate buffer with a p_H of 7. An 0.1 per cent solution of the histamine dihydrochloride was applied from the anode, as in the preliminary experiments. The enucleated globes were bisected in a frontal plane at the ora serrata.

The lens and vitreous were carefully removed from the anterior segment, and the reagents were dropped on the free inner surface of the ciliary body and on the posterior surface of the iris. The reagents for the oxidase reaction were freshly prepared, according to the modified technic of Winkler and Schultze.[15] This method gave more consistent results in our hands than the method recommended

15. Mallory, F. B.: Pathological Technique: A Practical Manual for Workers in Pathological Histology, Including Directions for the Performance of Autopsies and for Microphotography, Philadelphia, W. B. Saunders Company, 1938, p. 185.

by Schmelzer. The preparations were examined either with the wide field microscope or in frozen sections with a higher magnification.

The same technic was employed on eyes in which the penetration of penicillin across the barrier was studied after the use of the cyanide. A dose equivalent to 5,000 units of penicillin per kilogram of body weight was injected intramuscularly one hour after cyanide iontophoresis in one eye and after the control procedure with a 0.9 per cent solution of sodium chloride in the other eye. A dose of 8,000 units per kilogram was used when the control eyes were treated with phosphate buffer or with 0.1 per cent histamine dihydrochloride. Aqueous was withdrawn thirty minutes after the injection of penicillin. One-tenth cubic centimeter of aqueous was used for the assay of penicillin with the filter paper disk method, as described in a later part of this paper, and one-tenth was reserved for the nephelometric determination of the protein content. In several instances the penicillin level of the blood was examined at the same time. Then the animal was exsanguinated from the heart, and the eyes were dissected for the indophenol oxidase reaction. The record of the individual experiments contained, therefore, data on penicillin and protein concentrations in the aqueous and on the results of the test for Warburg's respiratory enzyme in the ciliary epithelium.

Results.—Complete, or almost complete, inhibition in the development of the color reaction in the ciliary epithelium was demonstrated in eyes which had been treated with cyanide thirty minutes to two hours before removal. The eyes subjected to the iontophoretic application of a 0.9 per cent solution of sodium chloride or of a 0.1 per cent solution of histamine dihydrochloride showed intensive blue staining of the ciliary processes. Densely packed blue granules of various sizes were seen in the ciliary epithelial cells, microscopically presenting the picture which has been described by previous authors.[16] The color did not develop as regularly in the eyes in which the phosphate buffer had been used.

When the eyes exposed to cyanide were compared with those treated with histamine, the average penicillin content of the former (0.418 unit per cubic centimeter of aqueous) was less than that of the latter (0.502 unit per cubic centimeter of aqueous), despite the inhibition of the respiratory mechanism in the ciliary epithelium and an excessive increase of the protein in the aqueous of the poisoned eyes. In this series, 8,000 units of penicillin per kilogram of body weight had been employed. The content of penicillin in the aqueous with inhibited respiration of the ciliary epithelium after injection of 5,000 units per kilogram of body weight was 0.23 unit per cubic centimeter, that is, twice the amount in the aqueous of eyes treated with sodium chloride (0.11 unit per cubic centimeter), even though the protein content of the former was about six times as great as that of the control eyes (tables 2 and 3). There was a moderate difference between the penicillin levels in the aqueous of eyes exposed to cyanide (0.39 unit per cubic centimeter) and that of the eyes treated with phosphate (0.284 unit

16. Seidel,[7] Schmelzer.[8]

per cubic centimeter); in the former the protein content of the aqueous was about four times that of the latter (table 4). The absolute amounts of penicillin in the aqueous of the series with the use of sodium chloride cannot be compared with those in the two other series because of the difference in the dose of penicillin.

TABLE 2.—*Penicillin Content of Aqueous and Indophenol Oxidase Reaction of Ciliary Epithelium Thirty Minutes After Intramuscular Injection of Sodium Penicillin Equivalent to 5,000 Units per Kilogram of Body Weight and Ninety Minutes After Iontophoretic Treatment of One Eye with Potassium Cyanide and of Other Eye with Sodium Chloride*

Units of Penicillin per Cc. of Aqueous		Indophenol Oxidase Reaction	
After Iontophoresis With		After Iontophoresis With	
Potassium Cyanide, 0.5%	Sodium Chloride, 0.9%	Potassium Cyanide, 0.5%	Sodium Chloride, 0.9%
0.30	0.10	—	+
0.15	0.10	—	+
0.20	0.15	—	+
0.22	0.12	—	+
0.30	0.10	..	..
Average 0.23	0.11		

TABLE 3.—*Protein Content of the Aqueous Ninety Minutes After Iontophoresis with Potassium Cyanide or with Sodium Chloride or After Corneal Bath with Sodium Chloride*

Milligrams of Protein/100 Cc. Aqueous		
After Iontophoresis with		After Corneal Bath with 0.9% Sodium Chloride
0.5% Potassium Cyanide	0.9% Sodium Chloride	
See 17 determinations, table 4.....	116.5	47.2
	94.4	44.2
	164.4	85.2
	106.5	54.0
Average....753.2	120.4	54.6

Comment.—The test for indophenol oxidase, which is based on the oxidation of colorless dimethyl-*p*-phenylenediamine to indophenol blue, demonstrates that Warburg's respiratory enzyme is abundant in the ciliary epithelium and lacking in the stroma. The secretory mechanism in the ciliary processes has been related to the large amount of the enzyme in the ciliary cells or to its unequal distribution between stroma and epithelium. According to Friedenwald and Stiehler, the latter causes a potential difference between these two structures of the

ciliary processes which is the source of an ionic current transferring water and cations from the stroma to the epithelium. The difference in potential and the current disappear when the cyanide-sensitive part of the respiratory mechanism in the ciliary epithelium is suppressed. Under this condition, only one component of the blood-aqueous barrier

TABLE 4.—*Penicillin and Protein Contents of Aqueous and Indophenol Oxidase Reaction of Ciliary Epithelium Thirty Minutes After Intramuscular Injection of Sodium Penicillin Equivalent to 8,000 Units per Kilogram of Body Weight and Ninety Minutes After Iontophoresis of One Eye with Potassium or Sodium Cyanide (2 Ma.; Five Minutes; from Cathode) or with Histamine Dihydrochloride (1 Ma.; Two and One-Half Minutes; from Anode)*

Units of Penicillin per Cc. Aqueous After Iontophoresis With		Mg./100 Cc. Protein After Iontophoresis With		Indophenol Oxidase Reaction * After Iontophoresis With	
0.5% Potassium Cyanide	Phosphate Buffer	0.5% Potassium Cyanide	Phosphate Buffer	0.5% Potassium Cyanide	Phosphate Buffer
0.18	0.2	308	140	..	..
0.34	0.42	660	135	—	±
0.38	0.30	938	258	—	+
0.83	0.36	...	...	—	±
0.52	0.21	926	135	—	+
0.20	0.20	...	...	—	—
0.30	0.10	826	130	—	—
Average 0.39	0.28	731.6	158.6		
0.5% Sodium Cyanide	0.1% Histamine Dihydrochloride	0.5% Sodium Cyanide	0.1% Histamine Dihydrochloride	0.5% Sodium Cyanide	0.1% Histamine Dihydrochloride
0.51	0.48	881	348	..	..
0.30	0.51	687	650	..	..
0.41	0.36	759	130	..	..
0.47	0.78	915	565	..	..
0.30	0.78	942	308	..	..
0.43	0.51	450	404	..	..
0.60	0.66	717	180	—	+
0.50	0.50	787	216	—	+
0.20	0.18	1,280	180	—	+
0.72	1.40	445	288	—	+
0.38	0.80	304	308	..	..
0.20	0.50	980	487	..	..
Average 0.418	0.502	762.2	338.7		

* In this column, — indicates a negative reaction; +, a positive reaction, and ±, a moderately positive reaction.

in the eye, the capillary endothelium, should remain unaffected. The permeability of this structure was not left unchanged, however, with the in vivo technic used in the present experiments, since the passage of proteins into the anterior chamber must have been caused, at least in part, by the increase in capillary permeability. A comparison of the penicillin levels of the eyes exposed to cyanide with those of the control eyes, which had received iontophoretic treatment with sodium chloride or phosphate buffer, is inconclusive because of the effect of the cyanide

on the intraocular capillaries. The use of histamine dihydrochloride resulted in a rise of the protein level which was comparable in some instances to that observed after cyanide iontophoresis, although it was lower in the majority of experiments. The penicillin levels in 5 experiments were about the same in the eyes treated with histamine and in those treated with cyanide; in 7 globes treated with histamine the penicillin level was higher, despite the relatively lower protein level in 4 of them. As the indophenol oxidase was almost fully inhibited in the eyes treated with cyanide and was not interfered with by the procedures in the eyes subjected to histamine iontophoresis, it is improbable that the epithelial component of the barrier exerts a restraining influence on the passage of the compound from blood to aqueous. The present experimental data point, rather, to an association of the penicillin levels in the aqueous with the permeability of the capillaries of the ciliary processes.

A more definite statement cannot be made without depletion curves for penicillin and protein. In the present experiment such curves could not be obtained because of the evanescent nature of the inhibition of Warburg's enzyme in the ciliary epithelium by cyanide.

Little is known of the action of cyanide on the vascular system, and no comprehensive work has been reported on the influence of the compound on capillaries. In the present experiments this influence was studied with the blue tetrazo dye T 1824, which combines and moves with serum albumin and with epinephrine in bleaching threshold doses. The results will be described in detail in another paper. Both tests proved that the capillaries of the limbus were affected by cyanide to a moderate degree. The visible escape of the dye into the tissue of the albinotic iris along the insertion of the ciliary processes on the posterior surface of the iris gave evidence of the great increase in the permeability of the ciliary capillaries due to the metabolic poison. The mechanism of this action of cyanide is still obscure. The inhibition by cyanide of adrenergic responses in certain smooth muscles, as demonstrated by Friedenwald and Buschke,[17] the interference with a theoretic cyanide-sensitive respiratory enzyme system in the capillary wall or a nonspecific irritation may be considered as a possible cause of the outpouring of protein.

Summary.—1. Cyanide was introduced into the anterior chamber by iontophoresis, and it remained there about two hours.

2. The concentrations which reached the ciliary epithelium were adequate to inhibit the cyanide-sensitive part of the respiratory mechanism in this structure for a period of one to two hours.

17. Friedenwald, J. S., and Buschke, W.: Effect of Cyanide and Other Metal Binding Substances on the Pharmacological Action of Epinephrine, Am. J. Physiol. **140**:367 (Dec.) 1943.

3. Simultaneously there was a steep rise in the protein level of the aqueous, presumably due to a pharmacotoxic action of the cyanide on the capillary endothelium.

4. A similar increase in the proteins of the aqueous occurred after histamine iontophoresis without inhibition of the cytochrome oxidase.

5. The penicillin content of the aqueous of eyes exposed to cyanide was greater than that of eyes treated with sodium chloride. Experiments with histamine indicated, however, that the increased penetration of penicillin across the blood-aqueous barrier in the eyes subjected to cyanide iontophoresis was probably due to an increase in capillary permeability, and not to an inactivation of Warburg's enzyme in the ciliary epithelium.

B. PENICILLIN LEVELS IN OCULAR AND OTHER BODY FLUIDS AFTER LIGATION OF RENAL VESSELS

Recent studies by Town and Hunt [2c] on the relation of penicillin levels in the blood to those in the aqueous confirmed earlier observations on the inadequate passage of penicillin from blood to aqueous and the effect of paracentesis in obtaining higher concentrations of the drug in the anterior chamber. Massive doses led to an appreciable increase in the penicillin level of the aqueous. The following experiments were conducted to gain more precise knowledge of the connection between the penicillin content of the blood and the levels in the aqueous, vitreous and spinal fluid by preventing renal excretion of penicillin. The depletion of penicillin in the blood in this condition was also considered.

Technic.—In a series of 8 rabbits, the hilar vessels of each kidney and the branches to the upper pole were securely tied with thick silk after the organs had been exposed by the lumbar approach. Eighteen to twenty-four hours later a solution of sodium penicillin in a dose of 8,000 units per kilogram of body weight was injected intramuscularly. One or three hours after the injection the penicillin content of the aqueous, vitreous, spinal fluid and blood serum was determined with the cup method. In the experiment with the three hour interval between the injection of penicillin and its determination in the body fluids, the blood level was usually examined one, two and three hours after injection.

Results.—At the selected time intervals, penicillin in the aqueous exceeded by far that in the spinal fluid and vitreous (table 5). In the one hour series the average of 6 observations on the aqueous was 1.25 unit per cubic centimeters, as compared with 0.23 unit per cubic centimeter for the spinal fluid and 0.14 unit per cubic centimeter for the vitreous. The average of 7 determinations of the penicillin level in the blood serum at the one hour interval was 17.4 units per cubic centimeter.

The average of 10 readings on the aqueous at the three hour interval (1.41 unit per cubic centimeter) was slightly higher than that at the one hour interval, whereas the readings on the spinal fluid (average,

0.14 unit per cubic centimeter) and on the vitreous (average, 0.08 unit per cubic centimeter) were lower at this time. The blood level after three hours showed a decrease to about 11.2 units, with great variations in the individual values. The gradients of the depletion curves were similar in 3 instances and considerably less steep in the fourth. In general, high penicillin levels in the blood serum, with a steady decrease during a period of three hours, secured in the aqueous relatively high and well retained penicillin concentrations, which were about 10 per cent of those in the blood serum, whereas only low, steadily decreasing amounts of penicillin were assayed in the spinal fluid and even lower amounts in the vitreous fluid.

TABLE 5.—*Penicillin Content of Aqueous, Vitreous, Spinal Fluid and Blood Serum After Intramuscular Injection of Sodium Penicillin Equivalent to 8,000 Units per Kilogram of Body Weight in Rabbits with Ligated Renal Vessels*

	Units of Penicillin per Cc.							
Hours After Injection	Aqueous		Vitreous		Spinal Fluid	Blood Serum		
	O D	O S	O D	O S				
1	0.34	0.48	0.14	Trace	0.24	8.50	.....	.....
1	1.18	1.36	0.14	Trace	0.22	17.00	.....	.....
1	2.12	2.00	0.13	0.22	0.23	20.00	.....	.....
Average	1.25		0.14		0.23	After (Hours)		
						One	Two	Three
3	2.24	1.58	0.14	0.16	0.27	.....	.....	19.70
3	1.48	1.04	Trace	Trace	Trace	18.10	11.30	7.00
3	0.62	0.86	Trace	Trace	0.12*	17.80	11.50	5.80
3	1.76	2.06	Trace	Trace	1.49*	21.80	19.50	10.00
3	1.28	1.14	Trace	Trace	Trace	18.60	14.90	13.70
Average	1.41		0.08		0.14	17.4	14.1	11.2

* The spinal fluid was mixed with blood; readings were discarded.

Comment.—The experiments on the mechanism of passage of penicillin across the blood-aqueous barrier and the relation between the drug levels of the blood and aqueous were carried out to examine whether the parenteral use of the antibiotic could be applied more effectively against infections of the eye. It was shown in the preceding section that the reason for inadequate amounts of penicillin in the ocular fluids after its systemic use probably does not lie in a selective retention of the substance by the blood-aqueous barrier.

The experimental data on renal blockage point to the importance of two factors as causes of the unsatisfactory drug levels in the eye. They are the steep decline of the penicillin content of the blood due to renal clearance within one hour after injection and the comparatively low concentration of about 0.1 unit per cubic centimeter in the blood

during continuous treatment. When excretion was prevented and a high peak blood level was maintained over a prolonged period, the penicillin level of the aqueous (1.41 unit per cubic centimeter) amounted to about 10 per cent of the penicillin content of the serum. It is evident, therefore, that serum levels below 0.5 unit per cubic centimeter cannot provide aqueous concentrations which are assayable with the cup method.

In contrast with the slight increase of the penicillin values for the aqueous during the observation of three hours was the decrease in the drug level of the vitreous in the same period. No explanation can be offered for this difference, as vitreous fluid did not inactivate the antibiotic in vitro. The decrease in the penicillin concentration of the blood of these experimental animals within three hours may be due in part to the diffusion of the compound into the tissue fluids. Small amounts of penicillin are secreted in the bile and saliva of nephrectomized animals, according to Cutting and co-workers.[18] These authors also suggested the possibility of some destruction of the compounds by reticuloendothelial cells.

Liebman and Newman,[19] in their studies on the distribution of sulfonamide compounds between blood and aqueous, reported that the average aqueous contents, expressed in percentages of the serum level, were 13.4 for sulfapyridine and 17.4 for sulfathiazole; these values, therefore, were in the same range as the corresponding figures for the penicillin experiments. Sulfadiazine penetrated three to four times as well as the two other sulfonamide compounds. A comparison of the rates of depletion of sulfonamide compounds and penicillin in the eye shows that in a four hour period the sulfadiazine content of the aqueous decreases to one-fourth, and the penicillin content to less than one-sixth, the original concentration. This difference between the speed of absorption of the two antibiotics in the aqueous is a second factor which may account for the comparatively moderate amounts of penicillin in the aqueous several hours after administration.

In general medicine the renal clearance of penicillin was depressed by the simultaneous administration of para-aminohippuric acid, which obviously competed with penicillin for the same renal excretory mechanism.[20] Iodopyracet injection U.S.P. ("diodrast")[21] and benzoic acid [21a]

18. Cutting, W. C.; Luduene, E. P.; Fiese, M.; Elliott, H. W., and Field, J., II.: Distribution and Fate of Penicillin in the Body, J. Pharmacol. & Exper. Therap. **85**:36 (Sept.) 1945.

19. Liebman, S. D., and Newman, E. H.: Distribution of Sulfanilamide and Its Derivatives Between Blood and Aqueous, Arch. Ophth. **26**:472 (Sept.) 1941.

20. Beyer, K. H.; Woodward, R.; Peters, L.; Verwey, W. F., and Mattis, P. A.: Prolongation of Penicillin Retention in the Body by Means of Para-

were also used for this purpose, with favorable results. Delayed absorption of penicillin was obtained with potassium sulfate and by the administration of penicillin in beeswax and peanut oil.[22] For the same purpose, ossein gelatin was used as a vehicle and the penicillin combined with a vasoconstrictor drug.[23]

In the present experiments, the relation between high penicillin levels in the blood and satisfactory concentrations in the aqueous was clearly demonstrated; Town and Hunt showed that the prolongation of low or medium drug levels in the blood did not influence the blood-aqueous ratio of the compound. It can be assumed, therefore, that procedures which reduce the renal excretion of penicillin after a massive dose, rather than those which delay absorption from the depot in the muscles, should be considered in the treatment of severe ocular infections.

Summary.—1. When the hilar vessels of the kidney and the branches to the upper pole were ligated, the parenteral injection of penicillin was followed by high blood levels, which declined slowly within three hours to about one-third the amount measured after one hour.

Aminohippuric Acid, Science **100**:107 (Aug. 4) 1944. Beyer, K. H.; Flippin, H.; Verwey, W. F., and Woodward, R.: Effect of Para-Aminohippuric Acid on Plasma Concentration of Penicillin in Man, J. A. M. A. **126**:1007 (Dec. 16) 1944. Beyer, K. H.; Verwey, W. F.; Woodward, R.; Peters, L., and Mattis, P. A.: Enhancement of the Plasma Concentration of Penicillin in Dogs by the Simultaneous Administration of Para-Aminohippuric Acid, Am. J. M. Sc. **209**:608 (May) 1945. Loewe, L.; Rosenblatt, P.; Alture-Werber, E., and Kozak, M.: The Prolonging Action of Penicillin by Para-Aminohippuric Acid, Proc. Soc. Exper. Biol. & Med. **58**:298 (April) 1945.

21. Rammelkamp, C. H., and Bradley, S. E.: Excretion of Penicillin in Man, Proc. Soc. Exper. Biol. & Med. **53**:30 (May) 1943.

21a. Bohls, S. W., and Cook, E. B. M.: Use of Aluminum-Penicillin Mixtures in Maintenance of Blood Levels of Penicillin: II. Combination of Delayed Absorption by Use of Aluminum-Penicillin and Renal Blockage with Benzoic Acid, Texas State J. Med. **41**:342 (Nov.) 1945.

22. Romansky, M. J., and Rittman, G. E.: A Method of Prolonging the Action of Penicillin, Science **100**:196 (Sept.) 1944; Penicillin: I. Prolonged Action in Beeswax-Peanut Oil Mixture; II. Single Injection Treatment of Gonorrhea, Bull. U. S. Army M. Dept., October 1944, no. 81, p. 43. Romansky, M. J.; Murphy, R. J., and Rittman, G. E.: Single Injection Treatment of Gonorrhea with Penicillin in Beeswax-Peanut Oil: Results in One Hundred and Seventy-Five Cases, J. A. M. A. **128**:404 (June 9) 1945. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, New England J. Med. **233**:577 (Nov. 15) 1945. Nichols, D. R., and Hanuz, E. A.: Prolonged Action of Penicillin in Mixtures of Beeswax and Peanut Oil, Proc. Staff Meet., Mayo Clin. **20**:403 (Oct.) 1945. Kirby, W. M. M.; Leifer, W.; Martin, S. P.; Rammelkamp, C. H., and Kinsman, J. M.: Intramuscular and Subcutaneous Administration of Penicillin in Beeswax-Peanut Oil, J. A. M. A. **129**:940 (Dec. 1) 1945.

23. Parkins, W.; Wiley, M.; Chandy, J., and Zintel, H. A.: Maintenance of the Blood Level of Penicillin After Intramuscular Injection, Science **101**:203 (Feb. 23) 1945.

2. The aqueous contained an average of 1.4 units per cubic centimeter at the three hour period. This was about one-tenth the penicillin concentration in the blood.

3. The level of penicillin in the vitreous and spinal fluid remained low despite its increase in the blood.

C. PASSAGE OF PENICILLIN FROM BLOOD INTO AQUEOUS AND VITREOUS IN OCULAR INFLAMMATION

Earlier studies, as well as those in the preceding experiments, suggested that the penetration into the aqueous was enhanced by dilatation of the capillaries. On this basis could be explained the effect of paracentesis,[2] intraocular injections of histamine,[1d] instillations of peroxide [3b] and the procedures described in the first part of this study. These experiments did not indicate, however, the extent to which an intraocular inflammation influenced the passage of penicillin across the blood-aqueous barrier. In the present study, a self-limiting inflammation of varying severity was produced by injecting staphylococcus toxin (staphylotoxin) into the vitreous. The clinical stage of the inflammatory process and the penicillin levels in the intraocular fluids were compared.

Technic.—In general, the staphylococcus toxin was prepared according to the technic of Leonard and Holm.[24] A strain of Staphylococcus aureus BD, supplied by the department of bacteriology, Columbia University College of Physicians and Surgeons, was grown in Kolle bottles on the semisynthetic, infusion-free medium recommended by Leonard and Holm. The inoculated bottles were placed in an atmosphere of 80 per cent carbon dioxide and 20 per cent oxygen, and the cultures were harvested after incubation for forty-eight hours. The content of the bottles was first filtered through filter paper and the filtrate centrifuged. The supernatant was siphoned off, adjusted to a p_H of 6.8 and filtered through a diatomaceous filter of medium porosity. The toxin was tested for sterility, and its hemolytic titer and dermonecrotic activity were determined according to general rules.

Tentative experiments showed the effect of intravitreal injections of the undiluted toxin. In the subsequent series, 0.05 to 0.1 cc. was injected into the vitreous of one eye of each rabbit in a group of 10 rabbits. The other eye was used as a control. The development and progress, as well as the regressive changes, of the inflammation were studied with the slit lamp and with the ophthalmoscope. At various stages of the inflammation, aqueous and vitreous fluid were examined for penicillin activity with the cup method half an hour after the intramuscular injection of sodium penicillin, equivalent to 8,000 units per kilogram of body weight. When the vitreous was examined, its appearance after withdrawal from the eye was recorded. Samples of blood for determination of penicillin were taken from the heart or ear shortly before withdrawal of the ocular fluids.

Results.—The staphylococcus toxin had a high titer of 4,000 minimum hemolytic doses. The dermonecrotic action was pronounced, but the minimal dermonecrotic dose was not determined. The eyes were

24. Leonard, G. F., and Holm, A.: A Method for Production of Staphylococcus Toxin and Toxoid, J. Immunol. **29**:209 (Sept.) 1935.

divided into two groups according to the stage of inflammation. In the eyes of the first group, signs of severe acute endophthalmitis were present, such as ciliary injection, exudate or dense flare and cellular deposits in the anterior chamber, extreme swelling and hyperemia of the iris and diffuse cloudiness in the vitreous. Details of the fundus could not be seen or were barely visible. The eyes of the second group showed less injection of the globes, a small number of cells and moderate flare in the aqueous and slight swelling of the iris. Details of the fundus were somewhat blurred by faint cloudiness in the vitreous.

Table 6 shows that the intensity of the acute inflammation had a definite bearing on the amount of penicillin in the aqueous, as it con-

TABLE 6.—*Penicillin Content of Aqueous and Vitreous Thirty Minutes After Intramuscular Injection of Sodium Penicillin Equivalent to 8,000 Units per Kilogram in Rabbits with Endophthalmitis Induced with Staphylococcus Toxin*

Type of Inflammation	Days After Injection of Staphylococcus Toxin	Units of Penicillin per Cubic Centimeter				
		Aqueous, in Inflamed Eyes	Vitreous, in Inflamed Eyes	Aqueous, in Control Eyes	Vitreous, in Control Eyes	Blood Serum
Severe	5	0.42	....	0.13	....	2.88
Severe	7	0.85	0.12	0.16	0.10	2.06
Severe	7	1.33	0.11	....	0.08	4.00
Severe	3	1.29	0.16	0.40	0.09	....
Severe	5	1.08	0.14	0.16	0.10	....
Severe	5	1.17	....	0.17	....	2.00
Average	..	0.98	0.13	....	....	....
Mild	6	0.39	....	0.08	....	....
Mild	12	0.12	....	0.11	....	3.70
Mild	11	0.39	....	0.12	....	2.90
Mild	10	0.46	....	0.12	....	4.00
Average	..	0.34	....	0.15	0.09	3.00

tained an average of almost 1 unit per cubic centimeter in the severely inflamed eyes. When the signs of the endophthalmitis had regressed greatly, the penicillin content of 0.34 unit per cubic centimeter was more than twice that of the normal eyes, with 0.15 unit per cubic centimeter. In all instances the penicillin level was higher in the aqueous of the inflamed eyes than in the control eyes.

Only slightly more penicillin was determined in the vitreous of the acutely diseased eyes than in that of the normal eyes. This observation was unexpected in the case of globes with newly formed vessels in membranes extending from the detached retina into the vitreous. The penicillin levels in the samples of blood which were withdrawn at about the same time as the intraocular fluids were not clearly related to the concentrations in the aqueous.

Comment.—Clinical reports on penicillin therapy of intraocular infections deal, in general, with cases in which the etiologic agent was unknown. The failure of systemic penicillin treatment, obviously, cannot be evaluated in these instances, as the presence of organisms susceptible to penicillin cannot be demonstrated.

Favorable observations on systemic penicillin therapy have not been recorded in cases of infections of the human vitreous; nor has this type of treatment been tested in a sufficient number of patients with acute ectogenous infections of the anterior segment. In experimental studies unsatisfactory results with intramuscular injection of penicillin were reported by Leopold [1d] when the vitreous was inoculated with cultures of sensitive organisms. Infections which Town and co-workers [25] produced in the rabbit's anterior chamber with a highly susceptible hemolytic streptococcus responded well so far as the corneal infiltration was concerned. On the other hand, corneal ulcers produced by a gram-negative, penicillin-sensitive rod were treated by Leopold and co-workers [26] more effectively by local means than by intramuscular administration of penicillin; and Miller and co-workers [27] noticed the failure of parenteral treatment of gonococcic infections of the anterior segment with penicillin in large doses. These inconsistent results may be explained by differences in the administered dose, in the character of the inflammation and in the susceptibility of the organisms.

Massive doses increased the level in experimental animals, but much higher values (about 1 unit per cubic centimeter) were determined for acutely and severely inflamed eyes in the current experiments. This amount was more than six times the average value for penicillin obtained in the aqueous of the normal eyes; in moderately inflamed eyes the penicillin level was about twice that in the controls. The dose in these experiments was in the range recommended for certain cases of endocarditis, meningitis and cerebrospinal syphilis.

The results of the present investigation indicate that infective foci in the vitreous will not be decisively influenced by systemic therapy, but high peak blood levels may be useful in supporting energetic local treatment, or even in substituting for it in the case of acute ectogenous infections of the anterior segment. The observations of Town and co-workers point to the value of this therapeutic approach, although

25. Town, A. E.; Frisbee, F. C., and Wisda, J. G.: Penicillin Control of Ocular Infection, Am. J. Ophth. **29**:341 (March) 1946.

26. Leopold, I. H.; Holmes, L. F., and La Motte, W. O., Jr.: Local Versus Systemic Penicillin Therapy of Rabbit Corneal Ulcer Produced by Gram-Negative Rod, Arch. Ophth. **32**:193 (Sept.) 1944.

27. Miller, C. P.; Bohnhoff, M., and Moeller, V.: Experimental Gonococcal Infection of the Rabbit's Eye: III. Treatment with Prophylactic and Therapeutic Agents, J. Infect. Dis. **77**:216 (Nov.-Dec.) 1945.

similar infections with the hemolytic streptococcus responded well to parenteral treatment with sulfanilamide. In view of the ineffectiveness of parenteral use of penicillin in cases of experimental gonococcic endophthalmitis of the anterior segment, however, no predictions can be made, especially with regard to the prognosis of infections with other penicillin-sensitive organisms.

Foci which are not exposed to the aqueous and which occur in deeper parts of vascularized tissue are accessible to the therapeutic agent circulating in the blood. On the basis of experimental evidence with massive doses of penicillin in inflamed eyes, better results may be anticipated in such conditions by increasing the usual clinical dose to that recommended for the aforementioned diseases. Local application of vasodilator substances may be a valuable adjuvant. The trauma of paracentesis in infected eyes of rabbits was found to be of definite disadvantage in the experiments of Town and co-workers. Their results suggest great caution in employment of this procedure.

Summary.—1. Acute, self-limiting endophthalmitis was produced by injecting staphylococcus toxin into the vitreous of rabbits.

2. The amount of penicillin determined in the aqueous after parenteral injection of massive doses of penicillin depended on the stage of the inflammatory process. With severe acute inflammations the aqueous level reached an average of 1 unit per cubic centimeter; it exceeded moderately that for normal eyes when the inflammation was in the regressive stage.

3. The penicillin level of the vitreous always remained very low under the experimental conditions studied.

II. SURFACE APPLICATIONS OF PENICILLIN IN OPHTHALMOLOGY

A. SOLUTIONS AND OINTMENTS

The common clinical procedures were utilized for topical ocular penicillin therapy. Depending on the site of the infection, preference was given to instillations of aqueous solutions or ointments, to the use of cotton packs or penicillin crystals, to corneal baths or iontophoretic introduction and to injection of solutions of penicillin under the conjunctiva or into the anterior chamber, lens or vitreous. In the treatment of certain surface infections with drops or ointments, the desirable concentration of penicillin in the vehicle and the frequency of use were matters of controversy. Concentrations from 50 to 20,000 units per cubic centimeter or per gram were recommended. Brown,[28] in his study

28. Brown, C. A.: Penicillin in Ophthalmology: Bacteriological, Experimental, and Clinical Evidence of Its Value, Including a Personal Series of One Hundred and Twenty-Five Clinical Cases, Brit. J. Ophth. **30**:146 (March) 1946.

of long-observed patients with conjunctivitis and blepharitis, proved that ointments containing 1,000 units per gram of base prevented relapses more readily than weaker preparations. More clinical evidence is necessary to show the advantage of high dosage in the treatment of corneal infections claimed by several authors (Juler and Johnson [29]) and questioned by others (Rycroft [1e]). Experience with penicillin therapy of well observed uncommon infections of the lids and conjunctiva is also too limited to permit general conclusions. In view of the debatable reliability of standard lesions in these parts of the eye of laboratory animals, little information can be expected from experimental studies; but the usefulness of local procedures is strongly suggested by the results of Leopold [26] and Robson and Scott.[30]

Experiments with various ointment bases and with various penicillin salts have been carried out [31] and results reported in regard to stability and penetration of the drug.[32] Data on the absorption from aqueous solutions are also available.[33] The question of an adequate frequency of instillations still meets with considerable uncertainty, as it depends on the morbid anatomy of the lesion and the susceptibility of the organisms to penicillin. Besides, little is known about persistence of penicillin action in the conjunctival sac after instillation. Milner [34] modified the Fleming slide cell method for estimating the penicillin content of conjunctival secretion at different intervals after instillation of penicillin drops or ointments. Reliable results could not be achieved in this laboratory with a similar technic. The quantities of the samples of tears could not be measured accurately with micropipets despite the use of lacrimators. The samples were frequently contaminated with penicillin-resistant organisms, which render the test valueless. It was soon obvious that the filter paper disk modification of the cup method,

29. Juler, F., and Johnson, G. T.: Use of Crystalline Penicillin in Corneal and Intraocular Infections, Brit. J. Ophth. **30**:204 (April) 1946.

30. Robson, J. M., and Scott, G. I.: Production and Treatment of Experimental Pneumococcal Hypopyon Ulcers in the Rabbit, Brit. J. Exper. Path. **24**:50 (April) 1943; Local Chemotherapy in Experimental Lesions of the Eye Produced by Staphylococcus Aureus, Lancet **1**:100 (Jan. 23) 1943; Experimental Streptococcal Lesions of the Rabbit's Eye and Their Treatment, Brit. J. Exper. Path. **25**:81 (June) 1944.

31. Keyes, J. E. L.: Penicillin in Ophthalmology, J. A. M. A. **126**:610 (Nov. 4) 1944. Minton, J.: Penicillin in Treatment of Common External Eye Infections, Brit. M. J. **2**:324 (Sept. 7) 1946. Merory, P. H.; McAnally, D., and Picard, C. W.: Penicillin for External Eye Infections, ibid. **2**:513 (Oct. 5) 1946.

32. von Sallmann, L.; Grosso, A. E., and Marsh, M. G.: Ophthalmic Penicillin Ointments, Arch. Ophth. **36**:284 (Sept.) 1946.

33. von Sallmann and Meyer.[1a] Bellows.[1c] Leopold.[1d]

34. Milner, J. G.: Penicillin in Ophthalmology, Brit. M. J. **2**:175 (Aug. 5) 1944.

described by Vincent and Vincent [35] and recommended also by De Beer and Sherwood,[36] was better suited to our purpose.

Technic.—Normal eyes of volunteers were used for the determination of the penicillin content of the tear fluid three, six and eight hours after instillation of penicillin drops in the right eye and of ointment containing the drug in the left eye. Eighty-four samples of tears were tested, including 8 control samples from untreated human eyes. Two drops of a solution of sodium penicillin containing 1,000 units per cubic centimeter was instilled into the lower cul-de-sac. The ointment, also containing 1,000 units of penicillin per gram, was pressed out of a collapsible tube on the surface of the lower fornix in the form of a double ribbon the length of the palpebral fissure. At the selected intervals of time, the lid borders of the eyes which had received the penicillin drops were cleaned with an 0.9 per cent solution of sodium chloride. Remnants of the ointment were removed from the surface of the lids by sponging with 80 per cent alcohol and with a solution of sodium chloride. Freshly cut onions were used as lacrimators. The first tears secreted were collected by two examiners at the same time from the two eyes by touching the tear fluid at the everted lower conjunctival fornix with the lower edge of a sterilized standard filter paper disk until its upper edge appeared dampened. Contact was avoided between the lid border and the filter paper, which was held in a sterile forceps. The disks were then placed equally distant from each other on seeded agar plates. Disks dampened in standard solutions of penicillin in a similar way were added to each plate so that triplicates of each dilution could be read. The zones of inhibition were evaluated as usual. Traces below 0.1 unit per cubic centimeter were judged from the density of the colonies in the area covered by the disk as seen under the wide field microscope.

Results.—It is evident from table 7 that the readings varied considerably within the same group of experiments on the same subject and among the individual subjects. In all eyes treated with an aqueous solution there was with time a continuous decrease in the assayable amount of penicillin. With 1 exception, in which slightly more penicillin was determined after three hours than after one hour, a similar decrease was observed in the eyes of 2 subjects treated with ointment. Several factors may account for the wide irregularities in the readings, but the main factor is undoubtedly the variation in the amount of tearing produced by the lacrimator and the consequent dilution of the penicillin in the sample. In general, the difference between the results with the two types of procedure was negligible. In the three and in the six hour series of experiment 2, the readings for the eyes treated with drops ran consistently higher than those obtained on the eyes with ointment. It is probable that in this experiment the ointment caused more irritation and loss of penicillin by reflex tearing. With 1 excep-

35. Vincent, J. G., and Vincent, H. W.: Filter Paper Disc Modification of the Oxford Cup Penicillin Determination, Proc. Soc. Exper. Biol. & Med. **55**:162 (March) 1944.

36. De Beer, E. J., and Sherwood, M. B.: The Paper-Disc Agar-Plate Method for the Assay of Antibiotic Substances, J. Bact. **50**:459 (Oct.) 1945.

tion, positive results were obtained with all samples of tears collected after six hours. The majority of tests made after eight hours also showed penicillin activity. Tears from untreated (control) eyes caused sparser growth beneath the filter paper disks, but the number of colonies exceeded those which were present after removal of the disks dampened in a phosphate buffer solution of p_H 6.8.

Comment.—The results of these experiments can be compared only in part with those of Milner, since he used solutions containing 500 units per cubic centimeter and an ointment with 100 units per gram and did not determine quantitatively the penicillin in the samples of conjunctival

TABLE 7.—*Penicillin Content of Tear Fluid at Various Intervals After One Instillation of Aqueous Solution or Ointment Containing Sodium Penicillin Equivalent to 1,000 Units per Cubic Centimeter or per Gram*

	Units of Penicillin per Cc. Tear Fluid							
Hours After Instillation	1		2		3		Untreated (Control) Eyes	
	O D Drops	O S Ointment	O D Drops	O S Ointment	O D Drops	O S Ointment	O D Drops	O S Ointment
3	0.07	0.53	1.71	0.14	0.11	0.16	0.00	0.00
	0.15	2.00	0.45	0.17	0.19	0.37	0.00	0.00
	0.19	0.36	0.47	0.285	0.41	0.10	0.00	0.00
	0.16	0.07	1.40	0.07	0.00	0.10	0.00	0.00
	....	....	0.47	0.5	....	....	....	....
Average...	0.14	0.54	0.95	0.23	0.18	0.18	0.00	0.00
6	0.09	0.11	0.46	0.09	0.11	0.11	....	....
	0.19	0.14	0.15	0.78	0.12	0.27	....	....
	0.08	0.23	1.42	0.325	0.09	0.00	....	....
	0.59	0.14	1.38	0.16	0.08	0.08	....	....
	....	....	0.69	0.14	....	....	....	....
Average...	0.23	0.15	0.82	0.29	0.10	0.11	....	....
8	0.14	0.30	0.13	0.41	0.00	0.10	....	....
	0.00	0.10	0.54	0.73	0.00	0.11	....	....
	0.07	0.00	0.27	0.08	0.09	0.07	....	....
	0.07	0.00	0.55	0.09	0.11	0.07	....	....
Average...	0.07	0.10	0.32	0.33	0.05	0.09	....	....

fluid. In contrast with Milner's results, there was no indication that penicillin remained longer in the conjunctiva after the use of ointment. In the present series, penicillin activity was observed in four fifths of the samples as long as eight hours after treatment. This finding suggests that instillations of penicillin can be sufficiently effective when given at intervals longer than are usually recommended, provided that the organisms are of average sensitivity and that the inflammation is not accompanied with epiphora. It is advisable to keep in mind the prolonged action of penicillin in the conjunctiva after one instillation when eyes are to be examined bacteriologically.

Summary.—1. The concentration of penicillin in tears was conveniently estimated with the filter paper disk method of Vincent and Vincent.

2. Tears of normal human eyes displayed penicillin activity in almost all instances six hours after instillation of a solution or an ointment containing 1,000 units per cubic centimeter or per gram. Eight hours after the treatment four fifths of the samples still possessed assayable amounts of penicillin.

3. The quantities of penicillin in the tears were about the same, and penicillin activity was observed for the same length of time regardless of whether ointment or solutions had been employed.

B. IONTOPHORETIC INTRODUCTION OF PENICILLIN

The value of cotton packs for stepping up the concentration in the anterior segment of the eye was discussed in a previous paper.[37] Since there was no disagreement on this form of therapy, no further studies were carried out in the present work. Opinions differ on the usefulness of introducing penicillin by iontophoresis. It was desirable, therefore, to investigate some factors operative in the penetration of penicillin into the eye under an impressed potential, the inactivation of penicillin due to changes of the p_H at the cathode, and the value of two types of clinical iontophoresis.

The principal objections to the rationale of penicillin iontophoresis have been voiced by Hamilton-Paterson.[38] On the basis of experiments with solutions of commercial penicillin, 25 and 50 units per cubic centimeter, the author arrived at the conclusion that penicillin is either a very poor conductor or a nonconductor. Without sufficient consideration to the extensive experimental data on this subject, Hamilton-Paterson expressed doubt whether a therapeutic concentration could ever be obtained in the tissue by means of iontophoresis. He commented further on the strong possibility that the penicillin would be destroyed by the products of electrolysis of other electrolytes present, and assumed that any attempts to introduce penicillin into the body by ionization were doomed to failure. It may be sufficient to counter with the results of a few experiments, which are easily reproducible.

1. *Conductivity of Sodium Penicillin.*—Ten milligrams of crystalline sodium penicillin G of a potency of 1,570 units per milligram[39] was dissolved in 3 cc. of conduction water (333 mg. per hundred cubic centimeters). The concentration of this solution approximates that

37. von Sallmann, L.: Penetration of Penicillin into the Eye: Further Studies, Arch. Ophth. **34**:195 (Sept.) 1945.

38. Hamilton-Paterson, J. L.: The "Ionization" of Penicillin, Brit. M. J. **1**:680 (May 4) 1946.

39. This penicillin was provided by Dr. O. Wintersteiner, of Squibb Institute for Medical Research. Although the preparation was analytically pure, the absence of small amounts of other penicillins (X, K and F) was not guaranteed. The content of such impurities was not likely to exceed 10 per cent.

used in ocular iontophoresis. Dr. Dan H. Moore, director of the electrophoretic laboratory, department of anatomy, Columbia University College of Physicians and Surgeons, determined the conductivity of the solution, with the following results:

$$\begin{array}{ll} KH_2O & 1.09 \times 10^{-6} \text{ mho} \\ K \text{ penicillin} & 290.00 \times 10^{-6} \text{ mho} \end{array}$$

$$\frac{K \text{ penicillin}}{KH_2O} = \frac{290.00 \times 10^{-6}}{1.09 \times 10^{-6}} = 266$$

That is, the conductivity of the water was increased 266 times by adding crystalline sodium penicillin G in a concentration of 333 mg. per hundred cubic centimeters.

2. *Influence of Change in p_H at Cathode on Activity of Penicillin.*—The destruction of penicillin by the shift of the p_H to the alkaline side when the cathode was immersed in the penicillin solution was discussed in a report from this laboratory in 1945.[40] The inactivation of penicillin by the increased p_H of the milieu around the negative terminal depends on the depth of immersion of the terminal, the density of the current, the duration of the treatment and the amount of penicillin solution in the applicator tube. In the previous study on the relation between the capacity of the applicator tube and the inactivation of the penicillin, the technic was not described, and a more detailed report seemed advisable.

Technic: Three types of applicators were selected for the tests: a Birkhäuser electrode used with 2 to 3 cc. of a solution of penicillin; a punctuated Stocker electrode which contained a cotton sponge saturated with 1 to 1.5 cc. of penicillin solution, and, finally, a thin cylindric tube which held 0.5 to 1.0 cc. of the electrolyte. The application time of five minutes, a current of 2 milliamperes and the concentration of penicillin (1,000 units per cubic centimeter) were constant. In the experiments with the Birkhäuser electrode the hydrogen ion concentration of the penicillin solution was estimated with indicator paper at the beginning of the procedure and after two and one-half and after five minutes. In this electrode the depth of immersion of the terminal was approximately 1.5 cm.

Results: As table 8 shows, the loss of antibiotic activity of the penicillin solution amounted to 60 per cent or more when very small quantities of the electrolyte were employed. It was previously pointed out that the destruction of the penicillin would be almost complete in the iontophoretic treatment of the root canals of the teeth because of the minute amount of solutions used in this method. The penicillin solution was prepared with a 0.9 per cent solution of sodium chloride. This solvent was slightly acid (p_H about 6), having been exposed for some time to the laboratory air. In corneal iontophoresis with the Birkhäuser or the van Heuven electrode, the p_H of the fluid almost reached the neutral point in two and one-half minutes and shifted in the

40. von Sallmann, L.: The Role of Iontophoresis with Antibiotics in Ocular Therapy, New York J. Dent. **15**:261 (Oct.) 1945.

following two and one-half minutes to a p_H between 8.6 and 9.4. The testing of samples from the solution in the applicator tube after five minutes of electrolysis indicated a loss of about 13 per cent of penicillin activity, that is, a negligible decrease of potency. It can be assumed that the inactivation of the compound will be in the same range as that with other electrodes of similar capacity.

3. *Factors Acting on Passage of Penicillin Through Cornea During Iontophoresis.*—It was demonstrated in many experiments that high concentrations of penicillin could be procured in the anterior segment of the rabbit and human eye by corneal iontophoresis. The penetration was about four to twenty times as great as with the corneal bath. It was also shown that the concentration of the penicillin solution, the milliamperage of the current, the length of treatment and the use of the anesthetic have a bearing on the amount of the compound introduced into the anterior chamber. It is not known whether there is an ion

TABLE 8.—*Percentual Loss in Activity of a Solution of Sodium Penicillin Equivalent to 1,000 Units per Cubic Centimeter After Iontophoresis for Five Minutes from the Cathode at 2 Ma. with Three Types of Applicator Tubes*

Type of Tube	Fluid Content of Tube, Cc.	Loss of Activity, per Cent
Birkhäuser	2-3	13
Stocker	1-1.5	58
Thin, conic	0.5-1	61

transfer (iontophoresis) or a transportation of the fluid with the undissociated salt (electro-osmosis), or whether the permeability of the cornea is increased by the flow of the electric current or a change in the p_H of the milieu. In the present experimental study, several factors are considered which may account for the relatively great amounts of the electrolyte in the anterior chamber after corneal iontophoresis. They are: (*a*) the effect of the flow of the electric current, (*b*) the changes in the hydrogen ion concentration in the electrolyte solvent, (*c*) the polarity of the terminal and (*d*) the tonicity of the penicillin solution.

(*a*) Effect of Flow of Electric Current from Cathode.

Technic: In 10 rabbits the right eye was treated iontophoretically with 0.9 per cent solution of sodium chloride for five minutes at 2 milliamperes from the cathode. The other eye received a corneal bath with this solution for the same length of time. After these procedures, both eyes were exposed to a corneal bath with a solution of sodium penicillin containing 2,000 units of penicillin per cubic centimeter for five minutes. The penicillin content of the aqueous was determined one hour later. The results were compared with those obtained by the iontophoretic introduction of penicillin in 0.9 per cent solution of sodium chloride containing 2,000 units of penicillin per cubic centimeter at 2 milliamperes for five minutes.

The changes in the p_H of the solutions due to the passage of the electric current were estimated with indicator paper.

Results: One hour after the sodium chloride bath and penicillin bath, the average penicillin concentration of the aqueous of the left eye was 0.39 unit per cubic centimeter, whereas the average penicillin content of the aqueous of the right eye, which had been exposed to iontophoresis with the solution of sodium chloride, followed by a penicillin bath, was about six times as great, with an average of 2.24 units per cubic centimeter (table 9). However, an average of 5.3 units per cubic centimeter was estimated in the aqueous one hour after a solution of

TABLE 9.—*Penicillin Content of Aqueous One Hour After Five Minute Corneal Bath with Solution Containing Sodium Penicillin Equivalent to 2,000 Units per Cubic Centimeter Which Followed Iontophoresis with Sodium Chloride of One Eye and Corneal Bath with Sodium Chloride of Other Eye*

Corneal Bath with Sodium Penicillin (2,000 Units per Cc.) for Five Minutes Following		
Iontophoresis with 0.9% Sodium Chloride at 2 Ma. for Five Minutes	Corneal Bath with 0.9% Sodium Chloride for Five Minutes	Iontophoresis with Sodium Penicillin (2,000 Units per Cc.) at 2 Ma. for Five Minutes
Units Penicillin per Cc. Aqueous		
1.6	0.4	6.4
1.6	0.4	6.4
1.6	0.8	3.2
1.6	0.2	6.4
3.2	0.1	3.2
0.8	0.4	6.4
1.6	0.2	...
0.8	0.4	...
6.4	0.4	...
3.4	0.2	...
Average.... 2.24	0.39	5.3

penicillin of the same strength was applied at 2 milliamperes for five minutes. The p_H of the solutions of sodium chloride and of sodium penicillin increased from 6.2 to a maximum of 9.4 during the passage of the current.

(*b*) Effect of Changes in Hydrogen Ion Concentration of the Bathing Fluid.

Technic: In a series of 6 rabbits the right cornea was subjected to a bath for two and one-half minutes of a 0.9 per cent solution of sodium chloride which had been adjusted with sodium hydroxide to a p_H of 9.4. This was followed by a corneal bath with a solution of sodium penicillin containing 5,000 units per cubic centimeter for five minutes; the same procedure was adopted for the left eye except that the solution of sodium chloride had a p_H of 6. Determination of penicillin in the aqueous was again carried out one hour after treatment.

Results: These experiments were undertaken in view of the possibility of a change in the permeability of the corneal epithelium due to brief exposure to a milieu of a p_H between 8.6 and 9.4. The p_H of the sodium chloride bath which preceded the penicillin bath had no significant effect on the permeability of the cornea for the antibiotic, as demonstrated by the penicillin content of the aqueous; it averaged 1.7 units per cubic centimeter for the right eyes and 1.6 units per cc. for the left eyes (table 10).

(*c*) Effect of Polarity of Terminal.

Technic: In a series of 10 rabbits, the right eye received cathode iontophoresis with a solution of sodium penicillin, equivalent to 5,000 units per cubic centimeter, for two minutes; the left eye was similarly treated with anode iontophoresis. In 10 additional eyes, a corneal bath was applied for the same length of time with a solution of penicillin of the same strength. The concentration of penicillin in the aqueous was determined one hour after the various procedures.

TABLE 10.—*Penicillin Content of Aqueous One Hour After Five Minute Corneal Bath with Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter Which Followed Corneal Bath with an Alkalized Solution of Sodium Chloride (p_H 9.4) on One Eye and Corneal Bath with Untreated Solution of Sodium Chloride (p_H 6) on Other Eye*

Units of Penicillin per Cubic Centimeter Aqueous After a Corneal Bath of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter for Five Minutes Following a Corneal Bath of Two and One-Half Minutes with	
0.9% Sodium Chloride at p_H 9.4	0.9% Sodium Chloride at p_H 6
Units Penicillin per Cc. Aqueous	
1.6	1.6
3.2	1.6
0.8	1.6
1.6	1.6
1.6	1.6
1.6	1.6
Average 1.7	1.6

Results: Iontophoreses with penicillin from the cathode was compared with that from the anode to clarify the nature of the transfer. When the length of the treatment was reduced to two minutes, the effect of the changes in p_H on penicillin was practically avoided. There was about four times as much penicillin in the aqueous after iontophoresis from the cathode (2.08 units per cubic centimeter) as after treatment from the anode (0.56 unit per cubic centimeter) (table 11). Only a small difference was evident between the amount of penicillin in the anterior chamber of eyes treated from the anode and that for the control eyes, which had received a simple bath with a penicillin solution of the same strength for the same length of time (0.38 unit per cubic centimeter).

(*d*) Effect of Tonicity of Penicillin Solution.

Technic: Solutions of sodium penicillin were made up accurately in a concentration of 2,000 units of penicillin per cubic centimeter in distilled water and in 0.9 per cent solution of sodium chloride. The right eye of 6 rabbits was treated iontophoretically at 2 milliamperes for five minutes with the strongly hypotonic solution, and the left eye, with the nearly isotonic solution. One hour after the procedure the aqueous was withdrawn for the determination of penicillin. In 8 rabbits corneal baths were applied similarly with isotonic and hypotonic solutions containing 5,000 units of penicillin per cubic centimeter.

The damage to the corneal epithelium due to the anesthetic and the penicillin solution in the two solvents was demonstrated by staining with fluorescein. The entry of fluorescein into the anterior chamber was quantitatively estimated in several instances with the slit lamp; the withdrawn aqueous was compared with standard dilutions of fluorescein.

TABLE 11.—*Penicillin Content of Aqueous One Hour After Cathode Iontophoresis, Anode Iontophoresis and Corneal Bath with Solution of Sodium Penicillin Containing 2,000 Units of Penicillin per Cubic Centimeter*

Units Penicillin per Cc. Aqueous After		
Cathode Iontophoresis, 2 Ma. for Two Minutes	Anode Iontophoresis, 2 Ma. for Two Minutes	Corneal Bath for Two Minutes
3.2	0.6	0.20
2.4	0.8	0.20
1.6	0.4	0.80
1.6	0.4	0.80
3.2	0.8	0.80
1.6	0.4	0.07
1.6	0.8	0.40
1.6	0.4	0.40
2.4	0.4	0.07
1.6	0.6	0.07
Average 2.08	0.56	0.38

Results: Far greater amounts of penicillin were measured in the aqueous when distilled water was used as a solvent instead of a 0.9 per cent solution of sodium chloride (table 12). The drug level was about 22.4 units per cubic centimeter one hour after the iontophoretic application of a strongly hypotonic solution, as compared with 5.3 units per cubic centimeter when a solution of sodium penicillin in saline solution had been applied. With the strongly hypotonic solution the irritation and the haziness of the corneal epithelium were more pronounced. The changes in p_H were essentially the same in the two types of solutions during the application of the electric current. Because of the lower conductivity of the hypotonic solutions, the impressed potential had to be increased by a few volts.

The effect of the tonicity of the penicillin solutions was also studied in experiments without applying the electric field. The penicillin con-

tent of the aqueous after the two procedures and the results of instillation of fluorescein as observed on the corneal epithelium and in the aqueous are presented in table 13. The drug level in the experiments with hypotonic solutions (8.67 units per cubic centimeter) was about 5.4 times as great as the level achieved with solutions of penicillin prepared in

TABLE 12.—*Penicillin Content of Aqueous One Hour After Corneal Iontophoresis at 2 Ma. After Five Minutes with a Solution of Sodium Penicillin Containing 2,000 Units per Cubic Centimeter of Distilled Water or 0.9 Per Cent Sodium Chloride*

Units Penicillin per Cc. Aqueous After Iontophoresis with Sodium Penicillin Containing 2,000 Units per Cc. in	
Distilled Water	0.9% Sodium Chloride
25.6	6.4
12.8	6.4
25.6	3.2
25.6	6.4
19.2	3.2
25.6	6.4
Average 22.4	5.3

TABLE 13.—*Penicillin Content of Aqueous and Results of Fluorescein Test One Hour After Corneal Bath with Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter of Distilled Water or 0.9 Per Cent Sodium Chloride*

Units Penicillin per Cc. Aqueous After Corneal Bath with Sodium Penicillin Containing 5,000 Units per Cc. in		Results of Fluorescein Test			
		On Cornea of Eyes Treated with Penicillin in		On Aqueous of Eyes Treated with Penicillin in	
Distilled Water	0.9% Sodium Chloride	Distilled Water	0.9% Sodium Chloride	Distilled Water	0.9% Sodium Chloride
12.8	1.6	+++	++	+++	+
6.4	1.2	++	++	++	+
3.2	1.6	+++	+	+++	+
4.2	...	+++	..	+++	..
2.4	0.2	++	+	++	+
4.8	0.3	++	+	+++	+
12.8*	3.2*				
12.8*	3.2*				
Average 8.67	1.6				

* Young rabbit.

0.9 per cent sodium chloride (1.6 units per cubic centimeter). This proportion was similar to that determined for the iontophoretically treated animals. For the latter, the individual readings were less erratic. The absolute values recorded in the iontophoresis and bath experiments could not be compared, since solutions of different strengths

were used to obtain readings in a convenient range. The table shows that the intensity of the staining of the cornea with fluorescein at the end of the corneal bath and that of the aqueous observed one hour later roughly paralleled the concentrations of the penicillin in the anterior chamber of such eyes.

Comment: It was advisable to investigate several phases of corneal iontophoresis and some factors involved in the clinical method, since the fundamental principles of the procedure were seriously questioned, chiefly on the basis of theoretic considerations. In contrast with the assumption of Hamilton-Paterson,[38] it was shown in experiments 1 and 2 that the sodium salt of crystalline penicillin G has the properties of a good conductor and that the decrease of the hydrogen ion concentration of the saline fluid during corneal iontophoresis with the cup electrode did not cause loss of penicillin activity of practical importance. As mentioned in an earlier paper, the latter observation could not be applied to types of iontophoresis in which the terminal is immersed in very little penicillin fluid.

The various previously described experiments on factors affecting the passage of penicillin through the cornea in iontophoresis did not offer a full explanation of the mechanism by which the electric procedure secured high penicillin levels in the aqueous, although several points were clarified. The interaction of ion transfer (iontophoresis) and the passive transport of the undissociated salt in solution by electro-osmosis is complicated. Penicillin is a strong organic acid with a p_K of 2.7 to 2.8. It can be assumed that in a 0.2 to 0.5 per cent aqueous solution most of the sodium salt is present in a dissociated form and will be transported as such in an electric field. In the later part of the treatment the cornea will carry a negative net charge and the aqueous will be charged positively relative to the cornea. In this period the fluid will be moved electro-osmotically toward the negative pole, which is placed on the cornea, that is, from the anterior chamber outward. It appears, therefore, that only the first of the two electrokinetic phenomena mentioned will be effective in the penetration of penicillin into the eye under the influence of the galvanic current.

Abramson, Moore, Gettner, Gagarin and Jennings [41] stated that a negatively charged, skin-reactive constituent of giant ragweed extract might be introduced by an electric field more efficiently with the positive pole. In view of these results, penicillin iontophoresis from the negative pole was compared with that from the positive pole. The penicillin ion was transferred from the negative pole in an amount

41. Abramson, H. A.; Moore, D. H.; Gettner, H.; Gagarin, J., and Jennings, L.: Isolation of an Unpigmented Skin Reactive Constituent from Extracts of Ragweed Pollen by Electrophoresis, Proc. Soc. Exper. Biol. & Med. **44**:311 (June) 1940.

four times as great as that from the positive pole. It can be concluded from these experiments that penicillin behaves in ocular iontophoresis as a negatively charged ion and that the conditions in iontophoresis of the skin are different from those in corneal iontophoresis.

In addition to other factors, complex diffusion forces are active in iontophoresis, as well as in the corneal bath, when the other experimental conditions are constant. They play a small part in the electric treatment, as the amounts of penicillin determined after the bath present one fourth to one twentieth of the quantities measured in the experiments under the influence of the electric field. This relation varies with the length of the procedure and the strength of the electrolytic solution.

A third group of factors consists of changes in the permeability of the cornea, or rather of the corneal epithelium, due to the procedure. It was shown in earlier experiments that the damaging effect of a local anesthetic on the epithelium has considerable bearing on the level of the drug in the aqueous. From the present study it can be deduced that a five minute flow of the electric current from the cathode through the 0.9 per cent solution of sodium chloride also increases dramatically the corneal permeability to penicillin. On the other hand, the low hydrogen ion concentration in the solution of sodium chloride in the last two minutes of the iontophoresis did not apparently cause an increase in the corneal permeability. The brief and moderate shift in the p_H of the salt solution was expected to be without influence on the corneal epithelium in view of the investigations of Cogan and Hirsch,[42] who found that "the epithelium maintained its normal barrier properties with variations in the p_H of 3.5 to 10.2."

The addition of a second salt (sodium chloride) to the solution of sodium penicillin resulted in a steep decrease in the measurable amounts of the antibiotic in the aqueous. Two mechanisms may operate under the conditions of the experiment to bring about this effect. The chloride ions will carry a part of the electric charges, and a smaller number of the penicillin ions will therefore be called on for the flow of the current. As the electric mobility of the penicillin ion is not known, the proportion of the two competing anions which pass through the cornea could not be estimated even if their concentrations were accurately determined. The second mechanism concerns the relation between the tonicity of the bathing solution and the permeability of the corneal epithelium. Solutions of sodium penicillin in distilled water caused a transient diffuse haziness of the corneal surface. Staining of the cornea with fluorescein and diffusion of the dye into the aqueous indicated the extent of the

42. Cogan, D. G., and Hirsch, E. O.: The Cornea: VII. Permeability to Weak Electrolytes, Arch. Ophth. **32**:276 (Oct.) 1944.

epithelial lesion, which could be roughly correlated with the increase of the penicillin level in the anterior chamber. When sodium penicillin in a 0.9 per cent solution of sodium chloride was employed as a bathing fluid on the cornea of rabbits for five minutes, the epithelium generally showed after staining with fluorescein a moderate number of green dots, comparable to those seen after instillation of the anesthetic. The usual concentrations of sodium penicillin in 0.9 per cent solution of sodium chloride are still slightly hypotonic to human tears, the degree of hypotonicity depending on the concentration of the fluid and the potency per milligram of weight of the penicillin salt. When distilled water was used as a solvent, a more extensive lesion of the epithelium could be well demonstrated with fluorescein. The studies of Cogan and Hirsch on the influence of phase solubility of drugs on their penetration through the cornea explained that the penetrability of the lipid-insoluble penicillin salt was greatly increased by the damage to the epithelial barrier.

The increase in the drug level in the aqueous after the use of penicillin in distilled water over that after its use in a nearly isotonic solution of sodium chloride was proportionately similar for the corneal bath and for iontophoresis. It seems, therefore, that in iontophoresis the transient lesion in the epithelial barrier due to the hypotonic fluid is more effective in procuring high drug levels in the aqueous than the relative increase of penicillin ions, which serve as carriers of the current. Further studies on animal and human eyes will show the extent to which the second salt can be omitted in order to improve the efficacy of the iontophoresis or of the corneal bath without causing damage and undue discomfort.

4. *Value of High Drug Levels in the Aqueous After Corneal Iontophoresis or Similar Procedures.*—Corneal iontophoresis is one of the nonsurgical methods which achieves a high penicillin level of about 10 to 20 units per cubic centimeter in the aqueous of rabbit [43] and of human eyes.[44] From the depletion curve, it may be assumed that the aqueous of rabbits retains 10 units per cubic centimeter or more of penicillin for several hours after treatment. Whether such a high, but transient, penicillin concentration will be advantageous in treatment of infections of the anterior segment will depend, among many other factors, on the susceptibility to penicillin of the infecting organism and the morbid anatomic character of the lesion. An attempt was made, therefore, to reproduce roughly in in vitro and in vivo experiments the conditions of such infections of the anterior chamber and to study the effect of varying concentrations of penicillin. In the in vitro study, cultures of

43. von Sallmann and Meyer.[1] von Sallmann.[37]

44. Wright, R. E., and Stuart-Harris, C. H.: Penetration of Penicillin into the Eye, Brit. J. Ophth. **29**:428 (Aug.) 1945.

Staph. aureus were exposed to concentrations of penicillin comparable to those in the aqueous, and their viability was observed at various intervals. In the in vivo experiments, culture dilutions of the same strain were injected into the anterior chamber of rabbits; treatment with iontophoresis or with corneal bath was initiated eight and twenty-four hours later, and the aqueous was withdrawn after twenty-four hours for plate counts.

Technic: 1. In vitro experiments: A strain of Staph. aureus which was inhibited by 0.1 unit of penicillin per cubic centimeter in the serial dilution assay was used as the test organism. Two-tenths cubic centimeter of a twenty-four hour culture, diluted 10^{-2} in broth, was added to 0.2 cc. of the solution of sodium penicillin in broth, so that the series contained 0.5, 1, 5 and 10 units per cubic centimeter. After two and four hours, respectively, the tubes were centrifuged and washed twice with ice cold isotonic solution of sodium chloride. The supernatant was finally replaced by 0.4 cc. of broth. The turbidity of the broth was observed after twenty-four and forty-eight hours. Each experiment, consisting of two parallel series and two control series, was repeated five times.

2. In vivo experiments: Both eyes of 9 rabbits were inoculated with 0.05 cc. of a twenty-four hour culture of the staphylococcus, strain H, diluted 10^{-3} in a 0.9 per cent solution of sodium chloride. The anterior chamber was inoculated after withdrawal of 0.1 cc. of aqueous with approximately 220,000 organisms, as estimated by plate counts. By thrusting a 30 gage needle obliquely through the cornea, leakage from the puncture wound was minimized. After eight or twenty-four hours the right eye was treated by iontophoresis with a solution of sodium penicillin in distilled water containing 5,000 units per cubic centimeter for five minutes at 2 milliamperes. The left eye received a five minute corneal bath with a solution of sodium penicillin of the same strength prepared in a 0.9 per cent solution of sodium chloride. After a twenty-four hour interval, the aqueous was withdrawn, and 0.2 cc. of the samples was incorporated in 15 cc. of melted nutrient agar for plate count. The course of the inflammation in the differently treated eyes was studied macroscopically and with the slit lamp.

Results: 1. In vitro experiments: In the experiments in which the staphylococcus cultures were exposed to penicillin for two hours, growth was noted in all but 1 tube (table 14). In this instance, 1 of the 2 tubes of the series containing 10 units per cubic centimeter was clear. With an exposure to 10 units per cubic centimeter for four hours, 9 tubes with the resuspended organisms remained clear, and 1 had growth at the observation time of twenty-four hours. In the following twenty-four hour period 3 additional tubes became turbid. Five units of penicillin per cubic centimeter prevented visible growth after a four hour exposure in only 1 of the 10 tubes of the series at the twenty-four hour interval. The other experiments with this, or weaker, dilutions of penicillin resulted in full growth of the centrifuged, washed and resuspended cultures.

2. In vivo experiments: The bacterial counts on the aqueous eight hours after infection showed, with 1 exception, a smaller number of viable organisms in the iontophoretically treated eyes (table 15). Only

in 1 instance were fewer colonies counted in the plate, which was seeded with aqueous from the eye with the corneal bath. The results for another rabbit could not be compared, since the iontophoretically treated eye presented more unfavorable conditions, owing to a corneal burn which was sustained during the procedure.

TABLE 14.—*Effect on Cultures of Staphylococcus Aureus of Exposure for Two and Four Hours to Penicillin in Various Concentrations*

Exposure Interval, Hr.	Units of Penicillin per Cc.	Effects on Cultures * at 24 Hour Period					48 Hour Period				
2	0.5	+	+	+	+	+	+	+	+	+	+
	1.0	+	+	+	+	+	+	+	+	+	+
	5.0	+	+	+	+	+	+	+	+	+	+
	10.0	+	+	+	+	±	+	+	+	+	+
4	0.5	+	+	+	+	+	+	+	+	+	+
	1.0	+	+	+	+	+	+	+	+	+	+
	5.0	+	±	+	+	+	+	+	+	+	+
	10.0	—	—	—	—	±	±	±	±	—	±

* The plus sign indicates growth in two tubes; the minus sign, no growth in two tubes; the plus-minus sign, growth in one tube and no growth in second tube.

TABLE 15.—*Plate Counts of Aqueous and Degree of Inflammation Thirty-Two Hours After Inoculation of Anterior Chamber with Staphylococcus Aureus Followed After Eight Hours by Iontophoresis with Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter of Distilled Water, or Corneal Bath with Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter of 0.9 Per Cent Sodium Chloride*

Number of Colonies		Degree of Inflammation	
After Iontophoresis	After Corneal Bath	After Iontophoresis	After Corneal Bath
2	9	Moderate	Moderate
9	21	Mild	Moderate
2	21	Mild	Very severe
1	4	Moderate	Severe
0	8	Mild	Severe
3	1	Moderate	Severe
6	6	Moderate	Severe
0	0	Mild	Mild
0	3	Mild	Severe

The effect of one treatment leading to a high peak penicillin level in the aqueous as compared with one treatment securing a medium level could be judged better from the clinical course of the inflammation. In 2 of 9 rabbits no significant difference was noted between the changes in the right and those in the left eyes. The iontophoretically treated

eyes benefited obviously from the high drug level in the 7 remaining instances. These included the eye which was traumatized by corneal burn and injury to the lens capsule during aspiration of aqueous. Under the conditions of the experiment, the advantage of high peak penicillin levels in the aqueous was demonstrated, therefore, by the course of the inflammation and suggested by the bacterial counts on aspirated aqueous.

Comment: It is known from extensive studies that many penicillin-sensitive organisms survive even after being exposed to the antibiotic substance over a prolonged period. Failures in clinical therapy may be due to this incomplete effect. The correlation between the concentrations of penicillin and its activity was reinvestigated by Rantz and Kirby,[45] who found, in contrast with earlier views, that "under certain circumstances the bacteriostatic activity of penicillin is proportional to its concentration." High peak penicillin levels in the blood, instead of the commonly recommended maintenance of a constant level, are favored for such localized infections as that present in endocarditis lenta.[46] It can be perceived that deeper-seated or less accessible infective lesions in the anterior segment of the eye will also benefit more from high peak drug levels in the aqueous and from a better penetration into the tissue than from a prolonged exposure to low and varying concentrations of penicillin.

The hypothesis that any treatment which secures high drug levels in the aqueous for several hours is of definite advantage is strongly supported by the results of the present in vivo and in vitro experiments. Injections of staphylococcus cultures into the anterior chamber of the rabbit eye without injury to the lens is sometimes followed by severe iridocyclitis leading to atrophy of the eye, but frequently only by a mild inflammation of self-limiting character. Heavy inoculums of 220,000 organisms did not change these results. For evaluation of the therapeutic effect of one treatment, the inflammatory signs in the first week were, therefore, more important than later observations, especially when additional therapy was employed to save the eyes. The bacterial counts on withdrawn and cultured aqueous are of limited value even in the earlier stages, since the number of organisms in the aqueous is not necessarily representative of the number of surviving organisms in other parts of the anterior chamber.

5. *Palpebral Iontophoresis.*—The preceding part of the study pertained mostly to corneal iontophoresis. In the original method of

45. Rantz, L. A., and Kirby, W. M. M.: The Action of Penicillin on Staphylococcus in Vitro, J. Immunol. **48**:335 (June) 1944.

46. Gerber, I. E.; Shwartzman, G., and Baehr, G.: Penetration of Penicillin into Foci of Infection, J. A. M. A. **130**:761 (March 23) 1946.

Wirtz,[47] sponges of cotton gauze were soaked with the electrolyte and were held in direct contact with the surface of the lids, the lid border, the conjunctiva or the cornea. This contact technic has been revived in recent years, and various types of elaborate applicators have been designed, especially for palpebral iontophoresis. They have been widely used for diseases of the lid border, conjunctiva and cornea, and even for deeper-seated lesions of the eye. The technic of palpebral iontophoresis has been advertised as being beneficial also in penicillin therapy of ocular infections. It was advisable, therefore, to investigate the fundamental principles of this method. Experiments were conducted to determine the content of penicillin in various parts of the lids, conjunctiva, cornea and aqueous after iontophoresis of the lid and simple moist dressings.

Technic: An applicator cup, supplied by the Teca Corporation, provided good contact for the cotton sponge on the carefully shaved, closed lids of rabbits. After instillation of 0.1 per cent nupercaine hydrochloride and 2 drops of the penicillin solution in the conjunctival sac, the electrode, containing the sponge soaked with 1.5 to 2 cc. of a solution of sodium penicillin, with a concentration of 5,000 units per cubic centimeter, was held on the closed lids. A current of 2 milliamperes was applied for five minutes to one eye; the second eye was similarly treated for the same length of time but without current (wet dressing). The milliamperage and the timing were selected to permit a comparison with the results of corneal iontophoresis. Immediately after the treatment, the lids were sponged with a 0.9 per cent solution of sodium chloride. The rabbits were killed one hour later. The lids were dissected and separated into an anterior skin-muscle layer and a posterior tarsus-conjunctiva plate. Extracts from the weighed layers of the lids, from the bulbar conjunctiva and from the cornea were prepared by grinding the samples with ignited quartz sand and with phosphate buffer of a p_H of 6.8. Buffer solution was used also for washing the mortar, pestles and weighing bottles. The extracts and washings were combined in a centrifuge tube and diluted to twenty times the weight of the respective tissues. The tubes were centrifuged, and quadruplicate samples of the supernatant were used for the determination of penicillin by the cup method. Throughout the procedure all materials were kept at a low temperature. Each experiment was repeated six times.

The changes in the p_H of the penicillin solution in the sponge and the partial inactivation of penicillin by the products of electrolysis were not investigated. A comparative series of experiments was conducted with the same technic, using as the electrolyte sodium sulfadiazine, which is not affected by changes in the p_H. A 5 per cent solution was applied, and the sulfadiazine content was determined in the various parts of the lids and eyes by the routine procedure of Bratton and Marshall. Each experiment was repeated five times.

Results: In the penicillin series, a moderate increase in the drug level was noted after iontophoresis in all tissues except in the conjunctiva bulbi as compared with the level after wet dressings (table 16). It will be remembered that far higher concentrations of penicillin were

47. Wirtz, R.: Die Ionentherapie in der Augenheilkunde, Klin. Monatsbl. f. Augenh. **46**:543, 1908.

obtained in the aqueous with corneal iontophoresis (19.2 units per cubic centimeter). The amounts of sulfadiazine in the various parts of the eye and its adnexa after iontophoresis of the lid did not exceed, in general, those found in the same structures after wet dressings (table 17). The readings for the cornea were so low and erratic that they could not be evaluated. The effectiveness of corneal iontophoresis as compared with that of the palpebral technic is illustrated by the high values obtained with the first method, that is, 119.92 mg. of sulfadiazine per hundred cubic centimeters in the cornea and 39.0 mg. of sulfadiazine per hundred cubic centimeters in the aqueous.

TABLE 16.—*Penicillin Content of Parts of the Lids, Conjunctiva, Cornea and Aqueous One Hour After Iontophoresis at 2 Ma. for Five Minutes or a Moist Dressing for Five Minutes with a Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter*

	Units Penicillin per Cubic Centimeter or Gram				
	Lid				
	Skin-Muscle	Tarsus-Conjunctiva Tarsi	Conjunctiva Bulbi	Cornea	Aqueous
			After Iontophoresis		
	47.10	8.23	1.90	41.30	0.75
	66.10	8.84	6.21	55.40	1.30
	50.42	3.96	7.76	70.30	2.00
	68.00	5.10	2.32	82.00	1.53
	70.00	4.90	1.65	80.70	0.48
	57.50	19.20	9.20	105.70	0.63
Average	59.85	8.37	4.84	72.57	1.12
			After Moist Dressing		
	74.20	1.83	2.83	0.07	0.22
	28.30	1.30	6.70	0.07	0.11
	38.60	2.83	4.84	66.20	1.99
	63.60	8.70	3.60	50.40	1.21
	17.30	0.07	1.27	0.07	0.07
	68.60	0.07	16.90	72.50	0.89
Average	48.43	2.47	6.02	31.55	0.75

Comment: In these experiments on rabbits, little advantage was gained by palpebral iontophoresis with penicillin in regard to the total content of the drugs in the parts of the eye examined. It was not possible, however, to study the distribution of the compounds in the various strata of the skin, sweat glands and sebaceous glands. The possibility cannot be excluded that the small amounts of the drugs were present predominantly in the glands after application of the electric field; such a distribution is suggested by Rein's [48] investigation of the transfer of colored cations and anions through the skin.

48. Rein, H.: Zur Elektrophysiologie der menschlichen Haut, Ztschr. f. Biol. **84**:41 (Jan.) 1926.

It might be argued that the penicillin was partially inactivated during the iontophoresis of the lid by the decrease of the hydrogen ion concentration in the latter part of the procedure, but the negative results with sulfadiazine iontophoresis indicated that the cause of the inadequate concentration in the tissues lay in the anatomic structure of the lid and conjunctiva and the rich supply of blood vessels.

The findings in the present series with sulfadiazine confirm the report of Clark, Strakosch and Nordlum,[49] who studied the passage of sulfonamide compounds through intact skin by iontophoresis and other means of local treatment. They described essentially the same penetra-

TABLE 17.—*Sulfadiazine Content of Parts of Lids, Conjunctiva, Cornea and Aqueous One Hour After Iontophoresis at 2 Milliamperes for Five Minutes or a Moist Dressing for Five Minutes with a 5 Per Cent Solution of Sodium Sulfadiazine*

	Mg./100 Cc. Sulfadiazine				
	Lid				
	Skin-Muscle	Tarsus-Conjunctiva Tarsi	Conjunctiva Bulbi	Cornea	Aqueous
			After Iontophoresis		
	19.27	Trace	Trace	1.513	Trace
	14.35	3.6	6.91	Trace	0
	5.17	0.70	Trace	Trace	Trace
	31.62	....	12.2	Trace	Trace
	28.62	....	12.4	Trace	Trace
Average	19.80	1.43	6.302	0.303	
			After Moist Dressing		
	18.97	0.471	3.33	Trace	Trace
	10.13	4.193	6.45	Trace	None
	10.71	Trace	Trace	Trace	Trace
	32.96	.....	11.61	1.25	Trace
	8.42	.....	3.76	4.04	Trace
Average	16.24	1.56	5.03	1.058	

tion for sulfathiazole when applied iontophoretically or by wet dressings to rabbit skin. Even prolonged applications for six hours did not lead to significant differences in the content of the compound with the two types of treatment. In the experiments with penicillin it was not feasible to extend the treatment over long periods because the compound would undoubtedly have been inactivated to a great degree by the alkaline milieu. Since considerably more of the sulfonamide compound was determined in the skin of dead rabbits after the iontophoretic procedure than after wet dressings, it could be assumed that the circu-

49. Clark, W. G.; Strakosch, E. A., and Nordlum, C.: Penetration of Sulfonamides Through the Intact Skin by Iontophoresis and Other Means of Local Application, Proc. Soc. Exper. Biol. & Med. **50**:43 (May) 1942.

lation of blood in the treated area and the barrier qualities of the living epidermis were responsible for the relatively low drug content after iontophoresis in the living animal.

Summary.—1. Sodium penicillin greatly increased the conductivity of electrically pure water and can, therefore, be considered a good conductor.

2. The shift of the hydrogen ion concentration in the penicillin solution beyond a p_H of 8 in the last one or two minutes of an iontophoretic treatment of the cornea with the usual cup electrode did not inactivate the drug to a degree of practical importance.

3. The good penetration of penicillin into the eye under the influence of an electric field was caused by ionic transfer, in addition to an increase in corneal permeability, due to the flow of the current from the cathode and to forces of diffusion.

4. Four times as much penicillin was determined in the aqueous one hour after iontophoresis from the cathode than after iontophoresis from the anode. This indicated that penicillin at a p_H of 6 to 8 behaved like a negatively charged ion.

5. A low tonicity of the penicillin solution radically facilitated the entry of the drug into the eye both with iontophoresis and with the corneal bath. Transient damage to the corneal epithelium, due to the hypotonicity of the bathing fluid, was the main factor in the increased penetration.

6. In vivo and in vitro experiments suggest that high peak levels in the aqueous sustained for several hours are desirable in the treatment of severe infections in the anterior segment of the eye.

7. Iontophoresis of the lid was only slightly more efficacious than simple wet dressings in obtaining increased and prolonged action of the tested antibiotics in various structures of the lids and the eye. Wet dressings may be useful in the treatment of certain surface infections of the lids, conjunctiva and cornea.

III. LOCAL INJECTIONS OF PENICILLIN

A. SUBCONJUNCTIVAL INJECTION

It was previously shown that relatively moderate penicillin levels could be obtained in the aqueous and traces in the vitreous of rabbits by subconjunctival injection if 2,500 units was employed.[50] Experimental infections of the vitreous with Diplococcus pneumoniae [51] and of the anterior chamber with Neisseria gonorrhœae [27] did not benefit from

50. Struble and Bellows.[1b] Leopold.[1d] von Sallmann.[37]

51. von Sallmann, L.: Penicillin Therapy of Infections of the Vitreous, Arch. Ophth. **33**:445 (June) 1945.

this therapy. Clinical reports [52] disclosed that such treatment gave satisfactory results in post-traumatic infections of the anterior segment. These observations suggested that beneficial results could be expected whenever the infecting organism was of high susceptibility to penicillin and if the infection had not extended to the lens. When strong solutions of penicillin were administered subconjunctivally, the attendant pain and discomfort could be overcome by adding an appropriate amount of procaine. Tests carried out in this laboratory confirmed the reports of Hesser and Golland [53] that the action of penicillin was not influenced by the addition of the anesthetic.[54]

B. INJECTION INTO THE ANTERIOR CHAMBER

The tolerance of rabbit eyes to injections of penicillin into the anterior chamber was tested in several laboratories. Despite the use of products of various origin and of differences in the technic, the reports showed satisfactory conformity.[55] A dose of 0.1 cc. of a solution of penicillin containing 2,000 units per cubic centimeter dissolved in 0.9 per cent solution of sodium chloride did not precipitate severe or prolonged reaction in the rabbit eye, provided that the samples were of high or medium purity. The penicillin salts manufactured at present in the large pharmaceutical houses can be considered a reasonably safe product when properly handled. Clinical experience points to the value of this type of therapy in cases of postoperative or post-traumatic iridocyclitis due to pyogenic organisms.[56] Irrigation of the anterior chamber is held to be valuable as a prophylactic procedure in cases of perforating injuries when infection of the anterior segment is probable. In treatment of experimental staphylococcic infections of the vitreous, partial success with the method was reported by Leopold [1d] in 4 of 10 eyes. Mann [3b] observed striking clinical results in cases of ectogenous infections extending into the vitreous from the replacement of aqueous with a solution of penicillin.

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52. Rycroft, B. W.: Subconjunctival Penicillin and Intraocular Infection, Brit. J. Ophth. **29**:501 (Oct.) 1945.

53. Hesser, F. P., and Golland, M.: Effect of Procaine on Inhibitory Factor of Penicillin, Mil. Surgeon **98**:47 (Jan.) 1946.

54. Serial dilutions of procaine hydrochloride containing 4, 2, 1, 0.5, 0.25, 0.125 and 0.06 per cent of the drug were added to appropriate mixtures of cultures of Staph. aureus in dilutions of sodium penicillin. The activity of penicillin was neither increased nor reduced.

55. (*a*) Dunnington, J. H., and von Sallmann, L.: Penicillin Therapy in Ophthalmology, Arch. Ophth. **32**:353 (Nov.) 1944. (*b*) Leopold.[1d] (*c*) Mann.[3b]

56. Ingalls, R. G.: Penetrating Wounds of the Cornea with Hypopyon Treated with Penicillin: A Case Report, Am. J. Ophth. **29**:1152 (Sept.) 1946.

C. INJECTION INTO THE LENS

The advantage of intralenticular injections of penicillin in eyes with the infective focus deep in the lens has been noted experimentally in lesions produced by pathogenic Staph. aureus [55a] and by strains of Clostridium welchii,[57] whereas corneal iontophoresis completely failed to check such infections.[58] Intralenticular injections have not been sufficiently used clinically to justify any conclusions as to their effectiveness in the human eye.

D. INJECTION INTO THE VITREOUS

It has been shown by several investigators that with injection into the globe adequate amounts of penicillin could be secured in the vitreous. A disparity in respect to reports on low penicillin concentrations in the vitreous obtained with other procedures can be accounted for by differences in the dose and in the method of removing the vitreous. A slow diffusion gradient of penicillin was demonstrated even in the semifluid vitreous gel of rabbits.[59] Samples of fluids aspirated from the vitreous are not representative of the whole, since varying activities can be expected in portions which are obtained before a uniform distribution of the salt has taken place in the gel. If the vitreous is removed *in toto* after dissection, admixture of aqueous from the posterior chamber, with a higher concentration of the drug, cannot be avoided. However, it is agreed that the low and inconsistent penicillin levels in the vitreous after nonsurgical administration are unsatisfactory. The experimental series with high peak levels in the blood or severe inflammation in the posterior segment, as reported in the first part of the present study, confirmed and extended this experience. Failures of such penicillin therapy of infections of the posterior segment have been observed both clinically and experimentally.

1. *Injection of Crystalline Penicillin into the Vitreous.*—The comparatively low toxicity of penicillin rendered the substance suitable for experiments with intravitreal injections.[60] Initial stages of experimental infections of laboratory animals and of similar lesions in the human

57. Hoskins, L. C.: Penicillin Therapy of Experimental Infections of the Lens and Vitreons with Clostridium Welchii, Arch. Ophth. **38**:301 (Sept.) 1947.

58. von Sallmann, L.: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infections with Staphylococcus Aureus and Clostridium Welchii, Arch. Ophth. **31**:54 (Jan.) 1944.

59. von Sallmann, L.; Meyer, K., and Di Grandi, J.: Experimental Study on Penicillin Treatment of Ectogenous Infection of Vitreous, Arch. Ophth. **32**:179 (Sept.) 1944.

60. von Sallmann.[51] Dunnington and von Sallmann.[55a] von Sallmann and others.[59]

eye [61] were treated successfully with this technic. The use of highly purified preparations was recommended from the first report. The earliest experimental series with penicillin compounds of various purifications—prepared in a small plant—indicated that the impurities in the salts caused a toxic reaction of the inner membranes of the eye.[59] Commercial preparations, which were tested later in this laboratory, were well tolerated by the rabbit eye when the amount of injected penicillin was limited to 100 units. Five times this dose resulted occasionally in circumscribed areas of retinal and choroidal destruction, which were identified only on histologic examination. These laboratory results were contradicted in a recent report of Mann on the deleterious effect of intravitreal injections of penicillin. The author used greater amounts, that is, 1,000 units of penicillin salt from various sources, among them Chas. Pfizer & Co. A batch from this pharmaceutical house was also used in the Knapp Laboratory and was found not to be injurious in lower concentrations. As the lot number of the preparation employed by Mann was not known, it was impossible to trace for more information. The severity and the extent of the chorioretinitis made it improbable that the greater dose of the injected compound produced the destruction. They suggested, rather, a contaminated sample or an unusual number of impurities, such as were present in some of the earlier products. The toxic effects of impurities could have been lessened to some degree by using a more dilute solution. One-hundredth the amount of penicillin administered by Mann controlled experimental infections of the vitreous which had been produced by various strains of pathogenic Staph. aureus and one strain of D. pneumoniae.[51] To gain more knowledge of the effect of pure preparations, further experiments, including thorough histologic examination of the globes, were conducted with commercial crystalline penicillin and with isolated crystalline penicillin G and crystalline penicillin K.

Technic: A 30 gage needle was used to inject 0.05 to 0.1 cc. of the saline solutions intravitreally. Two batches of the "crystalline penicillin sodium," supplied by Commercial Solvents Corporation, were tested; one batch had a potency of 1,430 units per milligram and the other of 1,590 units per milligram (lot no. 46071301), The latter contained 84 per cent of penicillin G. Data on the elementary analysis and on the comparative antibacterial assay were not obtainable. Doses of 200, 1,000 and 5,000 units were administered to 4 or 5 eyes for each concentration. The sodium salt of the isolated crystalline penicillin G (1,600 units per milligram) was prepared by Eli Lilly and Company (lot no. J-85-430). According to the assay of the Rockefeller Institute for Medical Research, the preparation appeared to

61. von Sallmann.[51] Feigenbaum, H., and Kornbluth, W.: Intravitreal Injection of Penicillin in a Case of Incipient Abscess of the Vitreous Following Extracapsular Cataract Extraction: Perfect Cure, Ophthalmologica **110**:300 (Nov.-Dec.) 1945. Weizenblatt, S.: Treatment of Acute Endophthalmitis: Report of a Case, Arch. Ophth. **36**:736 (Dec.) 1946.

contain about 3 per cent of material occurring in the K region and about 2.3 per cent occurring in the X region. On the preparations of penicillin K the following data were made accessible to us.

Sodium penicillin K (lot no. 7-12-46) of Chas. Pfizer & Co., Inc.
Elementary analysis

	Found %	Calculated for $C_{16}H_{25}O_4N_2SNa$ %
Carbon	52.84	52.73
Hydrogen	7.07	6.91
Nitrogen	7.66	7.69

Potency (based on 1,667 units per milligram for standard penicillin G
Turbidimetric assay

	Units/Mg.
Against Escherichia coli	198
Against Staphylococcus aureus	2,605

Oxford plate assay

Against Staph. aureus	2,075

Differential assay ratio
Bacillus subtilis: Staph. aureus.....0.36

Sodium penicillin K (lot no. RP 310-PI) of the Abbott Research Laboratories
Elementary analysis

	Found %	Calculated, %
Carbon	53.11	52.72
Hydrogen	6.7	6.9

Potency

	Units/Mg.
Against Staph. aureus	2,050
Against B. subtilis	750

Differential assay ratio:.....0.37

The salts were dissolved in a 0.9 per cent solution of sodium chloride and passed through a bacterial filter. A dose of 2,000 units was introduced in from 4 to 6 eyes.[62]

Results: Injections of "crystalline penicillin sodium," Commercial Solvents Corporation: The 14 eyes in which 200, 1,000 and 5,000 units were injected remained clinically free of inflammatory reaction except that caused by the trauma of injection. The following changes were considered of traumatic origin: the damage to the vitreous gel, as described by Loewenstein and Samuels[63] in 1918; the fine, spider-web opacities in the vitreous, probably due to minute hemorrhages, and the few cells circulating in the anterior chamber, with a transient increase in the Tyndall sign. No pathologic change in the fundus could be recognized despite the high dose. The retinal vessels appeared normal in caliber, and the fan of medullated fibers was distinct.

In general, the sections from globes injected with 200 and 1,000 units of crystalline sodium penicillin did not display inflammatory or degenerative lesions of the retina, uvea or optic nerve or damage to the lens. Red blood cells in moderate number in the vitreous were identified as the substrate of the fine, spider-web opacities which were observed clinically in several instances. In some eyes a small number of inflammatory cells and macrophages were seen in the region of the

62. One sample of crystalline sodium penicillin K and the sodium salt of crystalline penicillin G were made available through the cooperation of the Antibodies Study Section of the United States Public Health Service.

63. Löwenstein, A., and Samuels, B.: Ueber Glaskörperersatz: I. Experimentelle Untersuchungen, Arch. f. Ophth. **80**:500, 1911.

vitreous base or in other parts of the vitreous, which also contained faintly stained, droplet-like or amorphous debris. It could not be ascertained whether the debris was derived from the injected material. The number of red cells and wandering cells was not greater in the eyes receiving 1,000 units.

The 4 globes which had received the excessive dose of 5,000 units presented the following histologic picture: The anterior segment, including the lens, was free of pathologic change. The vitreous contained at its base, and in 1 instance axially, a few inflammatory cells, macrophages and red blood cells. The number of the cellular elements was not greater than in the eyes which had received 200 and 1,000 units. The retina and the optic nerve of 3 eyes did not show degenerative or inflammatory lesions. In the fourth eye there was a sharply outlined area of retinal atrophy, measuring about ½ disk diameter, adjacent to the upper margin of the nerve head.

Injections of crystalline penicillin G and K: The condition of eyes with 2,000 units of crystalline penicillin G was clinically similar to that of the eyes in the preceding series. A slight flare and a few cells in the anterior chamber and fine, spider-web opacities in the axial part of the vitreous were again ascribed to the trauma of injection. The changes in the aqueous disappeared within one week, and the opacities in the vitreous regressed more slowly.

Histologically, the eyes did not present signs of inflammation, except for an eye with round cell infiltration of the choroid proximal to the needle track. One or two small, circumscribed patches of partial retinal atrophy, of ½ to 1½ disk diameters, were visible in each of the 4 eyes. The rods and the outer nuclear and outer plexiform layers were missing here, whereas the elements of the second and third neuron layers and the external limiting membrane appeared intact. The cells of the pigment epithelium beneath the damaged area were partly depigmented or swollen. An apparently normal layer of medullary nerve fibers had prevented the clinical recognition of these small lesions.

The eyes which had received 2,000 units of the first sample of penicillin K presented signs of inflammation which could not have been caused by the trauma (table 18). For several days there were numerous cells in the aqueous and a diffuse veil in the vitreous. These changes were almost absent in the eyes in which the second sample was tested. A characteristic extensive lesion of the fundus was noted in all 6 eyes of this series. The retina was whitish gray twenty-four hours after the penicillin salt had been incorporated, mostly in the quadrant of the fundus which was closest to the point of the needle during the injection. The nerve head was blurred, and small hemorrhages in the retina and vitreous were seen in 3 eyes. The discoloration of the fundus decreased within the first week. At the end of this period grayish islands of

various sizes persisted as remnants of the extensive lesion. Dilatation and marked tortuosity of the retinal vessels were observed in the damaged sectors of the fundi of 3 eyes. With the regression of the grayish appearance of the retina, slightly irregular pigmentation of the eyeground developed in this area, and the fine striation of medullated fibers disappeared, leading to narrowing of the medullary wing in all instances. At this stage the fundus presented, therefore, the picture of a localized chorioretinal lesion with partial atrophy of the optic nerve.

TABLE 18.—*Local Toxic Effects Observed After Intravitreal Injection of Commercial Crystalline Sodium Penicillin and the Sodium Salts of Isolated Penicillin G and K*

Type of Penicillin	Potency, Units per Mg.	No. of Units Injected	No. of Eyes Receiving Injections	Observation Interval, Weeks	Clinical Observations	Histopathologic Observations
"Crystalline penicillin sodium" (Commercial Solvents Corporation)	.....	200	5	....	Fine, spider web opacities in vitreous; fundus normal	Few inflammatory cells and red blood cells in vitreous
Batch A.....	1,430	 1,000	.. 5	4-12		
Batch B.....	1,580	5,000	4	2-4	Fine, spider web opacities in vitreous; fundus normal	Few inflammatory cells in vitreous; small area of retinal atrophy in one eye
Sodium penicillin G (Eli Lilly & Co.)	1,600	2,000	4	3-4	Fine, spider web opacities in vitreous; fundus normal	Round cell infiltration around needle trace in one eye; small areas of partial retinal atrophy in all eyes
Sodium penicillin K Chas. Pfizer & Co.	2,000	2,000	2	2-4	Fine, diffuse opacities in vitreous; extensive grayish decoloration of retina with vascular changes, followed by circumscribed chorioretinal atrophy and partial optic nerve atrophy	Moderate number of inflammatory cells in vitreous; sectors of complete retinal destruction with obliteration of small retinal vessels and disappearance of medullated nerve fibers
Abbott Laboratories	2,050	2,000	4			

Histologic examination revealed a mild inflammatory response in the form of a moderate number of round cells in various parts of the vitreous. The degenerative changes in the retina were much more extensive than those seen after use of penicillin G and involved all layers. A thin, acellular glial membrane was the only remnant of the retina in several instances; in others, the structure of the inner layers could be identified. Small branches of retinal vessels appeared obliterated, owing to swelling and possible proliferation of the endothelial cells. The seat of the damage was either a broad sector or round areas of several disk diameters near the optic nerve. The pigment epithelium beneath the destroyed retina was depigmented, swollen or proliferated,

and the choroid occasionally showed an inconspicuous accumulation of round cells. In general, the inflammatory changes were negligible in comparison with the severe degenerative lesions of the retina. The histologic picture suggested that the vascular changes accompanied the retinal damage, rather than caused it.

Comment: The studies on the toxicity of penicillin by intravitreal injection were limited to relatively pure preparations, since nothing could be gained by investigating a great number of the usual commercial preparations, with their changing character. The experiments in this laboratory and those of Mann demonstrated that such batches from the same pharmaceutical concern usually could be well tolerated, or occasionally might produce destructive chorioretinitis. Mann also used crystalline products experimentally without ill effects as far as could be judged ophthalmoscopically; the results of histologic examinations were not reported. It was felt that information about the source, species and quality of the penicillin employed and a careful histologic study of treated eyes were necessary for evaluation and comparison of the data on toxicity. The damage of the retina, choroid and optic nerve with two samples of pure penicillin K was the most remarkable observation in this series; it suggested that some of the circumscribed lesions in the retina previously reported after the use of the common preparations of penicillin may have been caused by the presence of penicillin K in the product. The inferior antibiotic action of penicillin K in comparison with other forms,[64] together with the toxic action of two preparations shown in the present experiments, disqualifies this compound. The moderate toxic lesions in the inner membranes of the eye after the use of penicillin G could also have been caused by the presence of penicillin K in the sample. The low toxicity of this form compared favorably with the results of studies by Van Dyke [65] on penicillin G in general pharmacology.

It was shown that two batches of the commercial product (Commercial Solvent Corporation), "crystalline penicillin sodium," were noninjurious to the rabbit retina when a dose of 1,000 units was injected into the eye. Five times this amount also did not cause damage except for a small area of chorioretinal atrophy in 1 eye. With present knowledge, intravitreal injection of commercial crystalline penicillin with a fine needle (30 gage) can be considered as an effective and

64. Eagle, H., and Musselman, A.: Low Therapeutic Activity of Penicillin K Relative to That of Penicillins F, G, and X and Its Pharmacological Basis, Science **103**:618 (May 17) 1946. Coghill, R. D.; Osterberg, A. E., and Hazel, G. R.: The Relative Effectiveness of Pure Penicillins G, X, and K, ibid. **103**:709 (June 14) 1946.

65. Van Dyke, H. B.: Pharmacological Observations on Crystalline Sodium Penicillin, Proc. Soc. Exper. Biol. & Med. **56**:212 (June) 1944.

reasonably safe procedure in treatment of severe infections of the vitreous.

Summary: 1. Careful histologic examination proved that 2 samples of commercial crystalline penicillin could be injected into the vitreous up to amounts of 1,000 units without causing any retinal lesions. A minimal retinal damage was noted in 1 eye with the highest concentration, of 5,000 units.

2. One sample of crystalline penicillin G (2,000 units) was administered intravitreally, with a moderate toxic effect, which could be recognized histologically.

3. Two batches of crystalline penicillin K (2,000 units) produced severe degenerative changes in the retina and optic nerve when injected into the vitreous. It can be assumed that the destructive effect was produced by the penicillin compound, and not by residues of agents used for its isolation.

2. *Intravitreal Injection of Penicillin and Antitoxin.*—In a previous paper [58] it was noted that inflammatory changes in the posterior segment of the globe frequently led to the development of strands in the vitreous after the staphylococcic infection had obviously been checked by penicillin. Retinal folds, either circumscribed or amounting to extensive retinal detachment, were ascribed to the traction of these strands. It was assumed that the continued presence of preformed bacterial toxins might have aggravated the residual inflammation, although the organisms probably had been eliminated.

On the basis of this assumption, the clinical and histologic changes produced by injecting staphylococcus exotoxin were studied in preliminary experiments. These were followed by attempts at topical treatment with penicillin combined with homologous antitoxin. The effect of the combined treatment was compared with that of treatment with penicillin alone. The investigation was extended to local treatment with penicillin and antitoxin of vitreous infections with D. pneumoniae type III.

Technic: The staphylococcus toxin was prepared, and its hemolytic and necrotizing properties were tested, as described in the experiments in the first part of this paper. Injections of 0.05 to 0.1 cc. of the filtrate were made into the vitreous. Most of the 10 eyes were observed for twelve weeks.

Rabbits were immunized in accordance with general practice with a toxin derived from the same strain of Staph. aureus BD as was used for the ocular infections. The antitoxin titer of the serum was tested at suitable intervals; serums with titers of 13, 19 and 20 antitoxin units per cubic centimeter were finally employed for treatment after passage through a diatomaceous filter. A preservative was not added. The intravitreal therapy consisted in the injection of 0.1 cc. of a solution which contained 100 units of penicillin and 1.0 to 1.8 antitoxin units. The control eyes received 100 units of penicillin. The solutions were administered six hours (in 3 rabbits), eight hours (in 5 rabbits) and twenty-four hours (in 6 rabbits)

after injection of 0.05 cc. of Staph. aureus BD in a 10^{-3} to 10^{-4} dilution of a twenty-four hour broth culture.

Pneumococcus antitoxin in rabbit serum, with a titer of 4.58 micrograms of antibody nitrogen per cubic centimeter, was supplied by the laboratory of Dr. M. Heidelberger, department of medicine, College of Physicians and Surgeons. The "merthiolate" preservative was dialyzed against 0.9 per cent sodium chloride, and the serum was then passed through a microfilter under centrifugation. The infection of the vitreous of 6 eyes was made with 0.1 cc. of a 10^{-3} dilution of a strain of D. pneumoniae type III [66] and was inhibited by 0.0125 unit of penicillin per cubic centimeter. The treatment consisted in injecting the same dose of penicillin (100 units) as that used in the experiments with staphylococcic infection eight hours after inoculation. The dose of the antitoxin-penicillin fluid had a titer of about 0.4 microgram antibody nitrogen.

Results: Acute uveitis followed the injection of the staphylotoxin into the vitreous. The inflammatory signs in the anterior segment subsided after several weeks; posterior synechias or partial occlusion of the pupil remained. With the exception of 1 eye, posterior cortical cataract developed. Strands in the vitreous, partial or total retinal detachment and atrophy of the medullated fibers were seen clinically in the later stages, when the diffuse cloudiness had disappeared from the vitreous. The histologic study revealed strands of vitreous in 8 of the 10 globes. The strands varied from delicate to heavy and were often anchored to the retina around the disk or in a peripheral area. There were observed either steep retinal folds or total or partial retinal detachment, obviously produced by shrinkage of the membranes. The destruction of the retina was in most instances widespread and involved either all retinal layers or the neuroepithelium predominantly. The nerve had been affected by the traction of the strands to a variable degree. The presence of posterior cortical cataract was confirmed histologically. Foci of inflammatory cells remained in the ciliary body or the choroid of 3 eyes.

When treatment was initiated six hours after injection of the culture of staphylococci, the infection was controlled in the 3 eyes treated with penicillin and antitoxin, as well as in the 3 eyes treated with penicillin alone. No essential difference between the two groups was noted histologically. In the short interval between inoculation and treatment no strands developed in the vitreous. Inflammatory cells were present in moderate numbers three to four weeks after each type of therapy.

In the eyes treated eight hours after inoculation, the infection was not checked in 1 of 5 eyes with penicillin therapy, and in 2 of 5 eyes with the combined therapy. One of the eyes successfully treated with penicillin and antitoxin had severe optic neuritis, and 2 had fine strands

66. The lyophilized culture (36321) was obtained from the New York State Department of Health, which furnished the following data: The strain was isolated from a specimen of pus from a patient with acute mastoiditis, and its virulence for rabbits was demonstrated by intravenous injection.

in the vitreous. One of the eyes treated with penicillin alone also showed formation of strands.

Panophthalmitis with perforation or an abscess in the vitreous developed in the 12 eyes in which treatment was delayed twenty-four hours. Panophthalmitis with early perforation occurred in 4 of the eyes treated with penicillin and in 2 of the eyes treated with penicillin and antitoxin. The rest of the globes showed clinically and histologically the picture of an abscess of the vitreous.

The endopthalmitis in the 6 eyes into which were injected D. pneumoniae and which were treated after eight hours generally ran an unfavorable course. Five weeks after treatment extensive inflammatory changes were observed in all eyes, and foci of round cells were seen in the uvea. Shrinking membranes in the vitreous led partly to retinal detachment or to inward displacement of the nerve head. These lesions were more pronounced in the eyes treated with penicillin and antitoxin.

Comment: The combined action of antitoxin serums and penicillin was studied in infections with various toxin producers, the antibotic being directed toward inhibition of the growth of the offending organism and the antitoxin to neutralization of the toxin formed. Encouraging results of this therapy were reported in cases of gas gangrene [67] and of diphtheria.[68] The resemblance of the endophthalmitis produced by staphylococcus toxin to the lesions present in the vitreous and retina after effective penicillin therapy of staphylococcic infections suggested the combining of penicillin with specific antitoxin serums. The results were unfavorable. In none of the three groups of the staphylococcic infections was the course of the inflammation significantly altered by the combined treatment. It may be that the introduction of the serum as an excellent nutritive agent counteracted a possible beneficial effect.

In the tentative experiments with pneumococcic endophthalmitis the results were even less satisfying with penicillin and antitoxin than with penicillin alone. The infection with the strain of D. pneumoniae used in this series responded less favorably to penicillin than the strain which had been employed in a previous experimental series. As the

67. McIntosh, J., and Selbie, F. R.: Combined Action of Antitoxin and Local Chemotherapy on Cl. Welchii Infection in Mice, Lancet **2**:224 (Aug. 21) 1943. Evans, D. G.; Fuller, A. T., and Walter, J.: New Drugs Active in the Chemotherapy of Experimental Gas Gangrene, ibid. **2**:523 (Oct. 21) 1944. Siebenmann, C. O., and Plummer, H.: Chemotherapy and Antitoxin Therapy of Experimental Cl. Welchii Infection in Mice, J. Pharmacol. & Exper. Therap. **83**:71 (Jan.) 1945.

68. Ercoli, N.; Lewis, M. N., and Moench, L. J.: The Antibacterial Activity of Penicillin in Experimental Infections of Mice with C. Diphtheriae, J. Pharmacol. & Exper. Therap. **84**:120 (June) 1945. Young, R. G., and Mood, G. M.: Effect of Penicillin on Infection of Guinea Pigs with Corynebacterium Diphtheriae, J. Bact. **50**:205 (Aug.) 1945. Long, D. A.: Penicillin and Diphtheria, Correspondence, Brit. M. J. **1**:773 (May 18) 1946.

susceptibility of the former to penicillin was greater than in the older series, the larger inoculum (0.1 of a 10^{-1} dilution, instead of a 10^{-3} dilution) may have resulted in the unsatisfactory course.

Summary: 1. Injections of staphylococcus toxin into the vitreous of rabbits produced lesions similar to those observed in eyes treated successfully with penicillin.

2. Intravitreal injections of a mixture of a homologous antitoxin and penicillin were no more beneficial to the course of an experimental staphylococcic infection than was treatment with penicillin alone.

3. An endophthalmitis caused by D. pneumoniae type III reacted less favorably in tentative experiments to injections of penicillin and antitoxin than to penicillin alone.

IV. GENERAL CONCLUSIONS

The present study extended over several phases of the parenteral and local use of penicillin in ophthalmology. The failure of penicillin to pass the blood-aqueous barrier in adequate amounts during systemic therapy could not be related to a selective transfer through the ciliary epithelium or to a restraining effect of the epithelial membrane; it was shown, rather, to be related to the functional states of the capillary wall, to the steep decrease in the drug level in the blood by rapid renal excretion and, in a moderate degree, to the speed of absorption of the substance from the aqueous.

The negligible role of the ciliary epithelium in the mechanism of the passage of penicillin across the barrier was demonstrated by inhibiting the cyanide-sensitive respiratory enzyme system and was further suggested by the distribution of penicillin between blood and aqueous when renal clearance was prevented. The latter experiments also pointed to the value of a high and sustained penicillin content of the blood in securing satisfactory concentration of the drug in the aqueous. The importance of capillary permeability was shown by the great change in the aqueous-blood ratio of penicillin in various stages of a nonbacterial endophthalmitis.

In view of these experimental results, there is reason to believe that the best opportunity for utilizing the benefits of systemic penicillin treatment of severe ocular infections is offered in the administration of massive doses in the acute stages, aided by the simultaneous local instillation of vasodilators in cases of less violent inflammations; as an adjuvant may be considered the use of substances which decrease the renal output of the antibiotic by competing for the same excretory mechanism. General treatment may effectively supplement local penicillin therapy when the infective foci are not easily accessible by local methods.

In the study of the surface application of penicillin, the continuance of penicillin activity was usually observed in the tears for eight hours after one instillation of drops or ointment, suggesting that the frequency of treatment of external infections can be reduced without excessive tearing or secretion.

Several aspects of ocular iontophoresis with penicillin were studied. The claims of poor conduction of the compound and of a substantial destruction of the antibiotic by the shift of the hydrogen ion concentration, due to the products of electrolysis, were disproved in regard to corneal iontophoresis with applicator tubes of sufficient capacity. It was shown that the high penicillin content of the cornea and aqueous was procured by the effect of the flow of the current from the cathode on the barrier properties of the epithelium, by ionic transfer and, in a small part, by forces of diffusion. When solutions of low tonicity were employed, much more of the substance was observed in the aqueous, both after iontophoresis and after corneal bath, owing, however, to damage to the corneal epithelium. Palpebral iontophoresis with penicillin was far less valuable in achieving high drug levels in the anterior segment of the eye than was the corneal technic; in fact, little advantage was gained by the electric procedure as compared with the use of moist dressings.

It was of general interest to determine whether transient high peak concentrations of penicillin were advantageous in controlling infections of the anterior segment. In vitro and in vivo experiments gave evidence that better results could be expected from such high drug levels when the infecting organism was of medium sensitivity to penicillin. The observations appear applicable to iontophoresis, as well as to other means (cotton packs, injections) of obtaining a high penicillin content in the eye.

The usefulness of intraocular injections of penicillin had been shown previously in this and in other laboratories. The experimental results were verified by the clinical reports of several authors. The superiority of introducing the compound directly into the vitreous in treatment of infections of the posterior segment was demonstrated in experimental animals. The present painstaking investigations were concerned with the toxicity of excessively high doses of a commercial crystalline penicillin and of crystalline penicillin G and penicillin K, when injected into the vitreous space. A dose equivalent to 1,000 units of the commercial crystalline penicillin was used, without causing histologically recognizable retinal lesions. With a dose equivalent to 5,000 units of the commercial crystalline penicillin, a small, circumscribed area of chorioretinal atrophy was seen histologically in but 1 of all the serially sectioned eyes. A dose of 1,000 units is about ten times the amount which was effective in checking various experimental infections of the vitreous.

Injection into the vitreous of 2,000 units of one sample of isolated crystalline penicillin G gave rise to small lesions of the outer layers of the retina. When 2,000 units of the isolated crystalline penicillin K was injected, there was severe damage of the retina in all eyes, leading to localized retinal destruction and partial atrophy of the optic nerve. Penicillin for intraocular use, therefore, should be sterile, highly purified and relatively free of penicillin K. With observance of these requirements and the necessary technical care, direct injections of penicillin in the vitreous can be considered at present the most reasonable treatment of infections of the posterior segment.

Most of the data reported here were obtained in experiments on rabbits and were referred to common physiologic mechanisms. They may be correlated cautiously to conditions of the human eye so far as the fundamental concepts are concerned, but no conclusions can be drawn in regard to the quantitative data. A growing number of observations on the human eye corroborate some experimental findings, but more evidence, provided by well observed cases, is desirable to confirm or to disprove the clinical applicability of other experimental deductions.

NOTE.—Since this study was completed, an article by Sorsby and Ungar,[69] entitled "Pure Penicillin in Ophthalmology," has appeared.

The studies on the toxic effect of crystalline penicillin on the retina were extended to the types F and X and were amplified with respect to commercial penicillin. These experiments were not included in the original paper, for they had not been completed at the time of its submission. Penicillin F was available in such a small quantity that the injected dose had to be reduced to 1,000 units. Penicillin X was tested in the usual dose of 2,000 units and in the massive dose of 5,000 units. The experiments with commercial penicillin were completed by using 2,000 units. The technic of injection was the same as that previously described. The following data were available on the analysis of the two species of penicillin:

Penicillin X, pure, not crystalline (lot no. 76929) of Lederle Laboratories Division, American Cyanamid Company

Elementary analysis not obtainable

Differential assay ratio (B. subtilis to Staph. aureus)..... 1.2

Penicillin F, crystalline (lot no. 123 Bel 4) of The Upjohn Company

Chemical Analysis	Found	Calculated from $C_{14}H_{19}O_4N_2S\,Na$
Carbon, per cent.....	49.85; 50.118	50.28
Hydrogen, per cent.....	5.86; 6.08	5.73
Nitrogen, per cent.....	8.49; 8.41	8.38
Double bonds.....	1.02	1.00

Biologic assays

Potency	Units/Mg.
Against Staph. aureus.....	1,625
Against B. subtilis.....	1,075
Differential assay ratio..... 0.66	

69. Sorsby, A., and Ungar, J.: Pure Penicillin in Ophthalmology, Brit. M. J. 2:723 (Nov. 16) 1946.

The distribution curve (Dr. Lyman Craig, of the Rockefeller Institute for Medical Research) indicated that this material was free from penicillins X and K. A small deviation on the graph might be interpreted as indicating a small per cent of penicillin G.

The results are presented in table 19, in which the data on the previous series are also given. It is evident that penicillin F did not cause any damage to the retina or other parts of the interior of the eye when 1,000 units was introduced. Penicillin X was well tolerated in the dose of 2,000 units. Circumscribed lesions of the retina, as observed with the preparation of penicillin G used in this series, were absent. When the dose of penicillin X was increased to 5,000 units, there was a localized area of injury in the neuroepithelium in 1 of 4 eyes. The retina was unchanged after injections of 2,000 units of commercial

TABLE 19.—*Effect of Intravitreal Injection of Penicillins G, F, X and K and of Commercial Crystalline Sodium Penicillin on Retina of Rabbits*

Penicillin Preparation	Dose Injected, Oxford Units	Number of Eyes	Days of Observation	Appearance of Retina
Penicillin G.....	2,000	4	21-28	Small, circumscribed lesions on neuroepithelium in 4 eyes
Penicillin F.....	1,000	4	20-24	Normal
Penicillin X.....	2,000	4	7-31	Normal
	5,000	4	7-31	Normal in 3 eyes; small circumscribed lesions in neuroepithelium in 1 eye
Penicillin K (2 batches)	2,000	6	10-28	Extreme and extensive destruction of retina in 6 eyes
Commercial crystalline sodium penicillin....	200	5	24-60	Normal
Batch 1.....	1,000	5	24-60	Normal
Batch 2.....	2,000	4	10-28	Normal
	5,000	4	10-28	Normal in 3 eyes; small circumscribed lesions in 1 eye

crystalline sodium penicillin, a result which was expected from the infrequent occurrence of small lesions when 5,000 units had been used.

So far as may be concluded from the use of only one or two preparations of the various species of penicillin and of the commercial salt, penicillin X is the least toxic, but penicillin F cannot be included in this comparison, since it was introduced in a dose of only 1,000 units. The results with "crystalline penicillin sodium" of the Commercial Solvents Corporation compared favorably with those for penicillin X. It was recently shown that the antibacterial activity of the pure penicillin is lower than that of the impure preparations.[70] Even if the pure species were available for clinical use, no advantage would be

70. Hobby, G. L.; Burkhart, B., and Hyman, B.: Chemotherapeutic Action of Various Forms of Penicillin on Hemolytic Streptococcal Infections in Mice, Proc. Soc. Exper. Biol. & Med. **63**:296 (Nov.) 1946.

gained over treatment with commercial crystalline penicillin. If a high grade of this penicillin can be obtained and assurance can be given that it is practically free of penicillin K, the intravitreal treatment of infections of the posterior segment of the eye seems a safe procedure.

Dr. Dan H. Moore made the measurements of conductivity on a solution of penicillin G, and Miss P. Pfaff made serial preparations of 40 eyes in which penicillin was injected intravitreally.

The United States Public Health Service, National Institute of Health, Bethesda, Md., provided samples of penicillin G, F and K; the Abbott Laboratories supplied a preparation of penicillin K; the Lederle Laboratories Division of the American Cyanamid Company supplied the sample of penicillin X; the Commercial Solvents Corporation donated the preparation of "crystalline penicillin sodium," and the Teca Corporation constructed an application cup for contact iontophoresis in rabbits.

630 One Hundred and Sixty-Eighth Street.

CATARACT EXTRACTION BY THE SUCTION METHOD

A Review of Seventy-Five Cases

CHARLES I. THOMAS, M.D.
CLEVELAND

THERE is a great amount of literature available regarding the efficiency of the various types of cataract extraction. Although operators who have adhered to one method do not change easily, there should be more flexibility in the surgical technics used and emphasized in present day surgery. Though the procedure of cataract extraction is a matter of the individual surgeon's training, there are types of cataracts which are more efficiently removed by one method than by others. One can even say that it may be necessary to try several types of extraction on one lens in order to remove it as desired. Blaess [1] stated that individualism in surgical work is greatly overrated. It is more important to make the proper application of the technic most suitable to the case in question. I wholeheartedly agree with this opinion. The surgeon should adapt his methods to the case presented, having several procedures at his command and possessing the surgical judgment and flexibility befitting the occasion.

The intracapsular removal of the crystalline lens by means of the suction instrument has not yet been given its proper place of importance in cataract surgery. It is an extremely useful method, and one that is quite needlessly feared by many ophthalmic surgeons. Careful study of case reports by Nugent,[2] Wright,[3] Castroveijo,[4] Wolfe [5] and me

From the Department of Surgery, Division of Ophthalmology, Western Reserve University School of Medicine.

1. Blaess, M. J.: Removal of Cataract by Aspiration, Arch. Ophth. **19**:902 (June) 1938.

2. Nugent, O. B.: Cataract Extraction, Texas State J. Med. **32**:664, 1937; Oral Vacuum Control Value and Modified Green's Suction Cup, Tr. Sect. Ophth., A. M. A., 1933, p. 307.

3. Wright, R. E.: Cataract Extraction by the Barraquer Method, Brit. J. Ophth. **9**:57, 1925; The Barraquer Operation and Vitreous Changes, Am. J. Ophth. **7**:155, 1924.

4. Castroviejo, R.: Theoretical and Practical Study of the Intracapsular Cataract Extraction, Am. J. Ophth. **15**:406, 1932.

5. Wolfe, O. R.: The Barraquer Cataract Extraction, Am. J. Ophth. **18**:556, 1935.

fails to show any increase in risk to the patient by employment of this method. It should not be a routine procedure in all lens extractions, but it is extremely useful in the proper case. Every instrument table should have the necessary equipment to make this extraction possible. It has been found that, with this routine, intracapsular extraction has been made possible on many occasions when forceps extraction would have failed. One should also realize that the method to be used in intracapsular extraction may not be decided on until the anterior chamber has been opened and the character of the lens capsule studied. Then the surgeon should choose the method of extraction most likely to accomplish his purpose favorably.

HISTORY

The suction method, as it is today, evolved from an aspiration procedure by means of a hollow needle for removal of the contents of the lens. It was not until the twentieth century that a flat disk was attached to the aspiration needle in order to apply suction to the lens capsule and remove the cataract in its entirety. Antyllus,[6] during the Greek-Roman period (156 B. C.–576 A. D.); Tsabet ben Corra,[7] in the ninth century, and Alcoatin,[8] in the twelfth century, mentioned the removal of cataract by means of suction; but the method was applied to the cataracts of soft or liquid consistency which could be aspirated with the hollow needle. With the advent of the work of Daviel[9] and Brisseau,[10] this procedure fell into disuse, to be revived and modified a century later as a method of intracapsular extraction. Early in the twentieth century, Herz[11] introduced his suction cup, generating suction by means of the mouth; and Stoewer[12] devised a similar instrument, with which, however, suction was obtained by means of a rubber ball. Other models were made by Hulen,[13] Fisher,[14]

6. Antyllus, cited by Garrison, F.: History of Medicine, Philadelphia, W. B. Saunders Company, 1929.

7. Tsabet ben Corra, cited by Ribeiro.[21]

8. Alcoatin, cited by Ribeiro.[21]

9. Daviel, M.: Sur une nouvelle methode de guérir la cataracte par l'extraction du cristalin, Mém. Acad. roy. de chir. **2**:337, 1753.

10. Brisseau: Les recherches sur l'origine et les progrés de la chirurgie, Paris, G. Cavelier, 1734, p. 204.

11. Herz, cited by Saint-Martin, R.: L'extraction capsulo-lenticulaire de la cataract, Paris Masson & Cie, 1935.

12. Stoewer, P.: Demonstration eines Instrumentes zur Extraction der Linse in der Kapsel, Ophth. Gesellsch. **30**:296, 1902.

13. Hulen, V. H.: Vacuum Fixation of the Lens in the Extraction of a Cataract in Its Capsule, Tr. Sect. Ophth., A. M. A., 1911, p. 73.

14. Fisher, W. A.: Present Status of Intracapsular Cataract Operation, Illinois M. J. **65**:437, 1934.

Crosley [15] and Cruickshank.[16] In 1916 Barraquer [17] made his contribution of the eresiphake. This suction instrument was motor driven, and, as Barraquer stated, consisted of "a pneumatic forceps and a zonulatome." This instrument was adopted by various surgeons throughout the world, and modifications of the apparatus were then made by Dimitry,[18] Rochon-Duvignaud [19] and Arruga.[20]

By its development through the centuries, as so appropriately stated by Ribeiro,[21] "aspiration has triumphed. It is useful and in some cases indispensable."

INDICATIONS FOR THE SUCTION TECHNIC

The suction method can be used to the greatest advantage in cases in which (1) the lens is hypermature, (2) the capsule is tense, (3) the capsule has exfoliated, (4) the lens must be dislocated before it is tumbled or slid out of the fossa or (5) the capsule is friable and will not stand any tension.

Hypermature Lens.—When this condition is encountered, the extracapsular method of extraction is adequate, and has certainly stood the test of time; but if the intracapsular method is to be used, the suction method is ideal. In such a condition the lens capsule is usually tight and swollen, and ruptures easily if the forceps grasps it. When this type of lens is encountered, the suction cap, with its more evenly distributed traction on the capsule, offers the best method of removal of the lens.

Lens with Tense Capsule.—In another group of cataracts, the picture of hypermature lens is not present, but the capsule is tight and cannot satisfactorily be grasped with the capsule forceps without the probability of rupturing the capsule. Such lenses are ideally removed by application of suction. This condition is apt to occur in the younger

15. Crosley, E. R.: Intracapsular Extraction by the Vacuum Cup Method: Report of Fourteen Cases, Illinois M. J. **63**:519, 1933; Intracapsular Cataract Extraction by the Vacuum Cup Method, Am. J. Ophth. **15**:1147, 1933.

16. Cruickshank, M. M.: Phacoerisis, Brit. J. Ophth. **9**:321, 1925.

17. Barraquer, J. A.: Quelques indication de la phakoerisis, Clin. opht. **22**: 387, 1917; Phakoerisis, Arch. Soc. oftal. hispano-am. **17**:252, 1917; Dangers of Capsulotomy and Advantages of Complete Extraction, Arch. Ophth. **50**:307 (July) 1921; Phakoerisis, ibid. **51**:448 (Sept.) 1922.

18. Dimitry, T. J.: Vacuum Grasping Instrument for the Removal of Cataract in Capsule, Arch. Ophth. **9**:261 (Feb.) 1933.

19. Rochon-Duvignaud, cited by Saint-Martin, R.: L'extraction capsulolenticulaire de la cataract, Paris, Masson & Cie, 1935.

20. Arruga, H.: Extración intracapsular de la catarata, Arch. de oftal. hispano-am. **30**:593, 1930.

21. Ribeiro, R.: La aspiración al servicio del tratamiento de la catarata à traves de los siglos, Arch. Soc. oftal. hispano-am. **5**:434, 1945.

type of cataract, in which a tight zonule may be present. These zonular fibers are difficult to rupture, and the traction and counterpressure necessary to rupture the fibers are often so great that the capsule may, and often does, rupture before the zonule when the capsule forceps is applied. Hence, with application of the suction method tension is more evenly distributed on the capsule, with less likelihood of rupture.

Exfoliation of the Lens Capsule.—This condition requires removal of the lens, preferably by the intracapsular route. Owing to the degenerative changes that take place in the lens capsule, this structure disintegrates readily when attempts are made to grasp it with the lens forceps (Vogt,[22] Sobhy Bey [23]). The suction instrument, adhering to a larger area and distributing its lines of stress over a large area, is more likely to bring the lens out intact than is the capsule forceps. Because of the frequency of glaucoma capsulare (Sobhy Bey,[23] Vogt,[22] Busacca [24]), removal of all the capsular fragments is advisable; so whenever possible an intracapsular operation should be performed.

Aid in Dislocation of Lens.—In delivering the lens with the capsule forceps, it has been found useful first to dislocate the lens by means of the suction cup placed in the center of the lens and then to reapply the capsule forceps. This is applicable when the operator feels that the tension on the capsule is not causing sufficient progress in dislocation or when he believes that rupture of the capsule is imminent.

Friable Lens Capsule.—Another type of cataract for which the suction method is applicable is the senile nuclear and cortical cataract with a friable capsule. It is apparent at the outset that as soon as the capsule is grasped it will stand no tension. With these cataracts, if one prefers the intracapsular operation, the suction method is ideally applied.

ADVANTAGES OF THE SUCTION METHOD

According to Barraquer, there are three defects in the extracapsular method of extraction: (1) the necessity for pressure and its consequences; (2) instrumentation with the eye, to remove the remains of the lens, and (3) the retention of cortical material. He reasoned that any method by which the lens is removed without pressure and excessive instrumentation is the safest means of avoiding complications. On this principle, the author based the two advantages of the suction

22. Vogt, A.: Neue Fälle von Linsenkapselglaukom (Glaukoma capsulare), Klin. Monatsbl. f. Augenh. **84**:1, 1930.

23. Sobhy Bey, M.: A Contribution to the Study of Exfoliation of the Lens Capsule or Glaucoma Capsulo-Cuticulare with Anatomical Preparation, Brit. J. Ophth. **16**:65, 1932.

24. Busacca, A.: Anatomische und klinische Beobachtungen über die Zonulalamelle und ihre Ablösung von der Linse, Klin. Monatsbl. f. Augenh. **83**:737, 1929.

apparatus for removal of the lens over the capsule forceps, namely, the evener distribution of traction, and less counterpressure.

The drawing of the suction tip in place on the capsule of the lens (fig. 1) shows the lines of traction magnified and illustrates the large area over which this pull is exerted. This method not only lessens the likelihood of rupture of the capsule but also affords an easier removal of the lens itself by distributing the area of traction. This drawing may be compared with figure 2, showing the lines of traction on the lens capsule when the capsule forceps is used. Here, the entire weight of the lens and its attachments are suspended from a relatively small area.

Fig. 1.—Suction tip in place on the lens capsule, showing lines of stress.

The second advantage, that of less counterpressure, is based on the evener distribution of traction, and, consequently, the necessity of less pressure to produce the same effect. In one of the cases studied, this advantage was strikingly illustrated, as early in the extraction a bead of vitreous presented at the edge of the wound behind the lens but was not forced out because no counterpressure was necessary, and the lens was delivered by means of suction only. Immediate closure of the wound after the lens was removed prevented any complication.

PITFALLS IN USE OF THE SUCTION TECHNIC

Besides emphasizing the advantages of removal of the lens by suction, I wish to mention the pitfalls in this operative procedure and

to list the types of cases in which it is contraindicated. The pitfalls lie, first, in the improper selection of cases in which the method is to be used and, second, in loss of vitreous as a result of improper selection of cases, improper choice of instrument or faulty application of the technic. Proper selection of cases on the basis of the indications discussed earlier in the paper should be followed in order that the best results may be obtained. Loss of vitreous is often mentioned as a frequent occurrence. This complication should not be feared, however, if cases are selected properly and the instrument is applied with precision. I believe that the likelihood of loss of vitreous is much greater with motor suction than with the syringe type. The instant that the

Fig. 2.—Capsule forceps in place on the lens capsule, showing lines of stress.

disk slips from the capsule the suction is relaxed, whereas with motor suction another manipulation is required to stop the pull.

There should be less chance for loss of vitreous when suction is used under proper conditions than when the capsule forceps is used for intracapsular extraction. With the use of the capsule forceps, counterpressure is an important manipulation in bringing about the removal of the lens, and it is because of this procedure that vitreous is often lost. With the suction technic counterpressure is a relatively unimportant part of the procedure, and may or may not be used, depending on the case. Without counterpressure the possibility of loss of vitreous is lessened.

Improper application of the technic may lead to trouble. The comment has been expressed by various operators that in use of the suction instrument which I advocate there is a tendency for the suction

cap to slip off the lens. This likelihood can be lessened by observance of two factors: 1. In rotating or sliding the lens, the suction cap must be kept parallel with the body of the lens. Any tendency to change the angle of rotation or the parallel alinement of the lens and cap may easily cause the disk to slip from the lens capsule. 2. The lens must not be withdrawn too rapidly. Time must be taken to break the zonular fibers properly. If the suction cap does slip off the lens, it is simply replaced, and nothing is to be feared if the procedure is under control. Slipping occurs when the lens is dislocated and partially delivered.

CONTRAINDICATIONS TO THE SUCTION TECHNIC

Use of the suction instrument is contraindicated in several types of cases. When the following conditions exist, other, established, procedures should be resorted to in removing the lens: (1) fluid vitreous, when due to high myopia or the result of a chronic inflammatory process in the eye, and (2) dislocated lens, of either traumatic or congenital origin.

Fluid vitreous may be suspected to exist, and its presence be determined, before operation. Unfortunately, however, one may not be aware of its presence until the corneal section is made and vitreous begins to seep out. Suction is not advocated in such cases, as further and more rapid loss of vitreous may follow. One of the other procedures, such as that advocated by Kirby,[25] is more likely to be followed by successful removal of the lens.

In the case of a dislocated lens, the so-called margin of safety is small to begin with, and the application of the suction instrument may be difficult unless the lens presents immediately in the wound. Otherwise, sufficient resistance to the instrument is not present, and either vitreous may be drawn up with the syringe or the lens may be further dislocated. I then turn to one of the accepted methods of extraction.

OPERATIVE TECHNIC

It should be emphasized that with the suction instrument either the sliding or the tumbling technic may be employed in delivering the lens. However, it has been found that it is much more satisfactory to tumble a lens with suction than to slide it out. The suction is more likely to be released from the capsule if the latter method is used. However, the sliding technic is indicated with the suction instrument when the lens is dislocated easily and presents itself in the wound.

With the tumbling technic, one must rotate the suction cap in an arc parallel to the vertical plane of the lens. This is necessary to

25. Kirby, D. B.: Intracapsular Cataract Extraction, Am. J. Ophth. **25**:269, 1942.

insure continued even pull on the lens. In the performance of this method, the hand and wrist must be lowered as the cap is rotated, or improper rotation will tend to raise one edge of the suction cup from the capsule of the lens.

The instrument advocated for the suction method of extraction is my modification of the Dimitry [18] suction instrument, illustrated in figure 3.[26] This apparatus consists of the Dimitry syringe modified to increase the suction, a 6 inch (15 cm.)

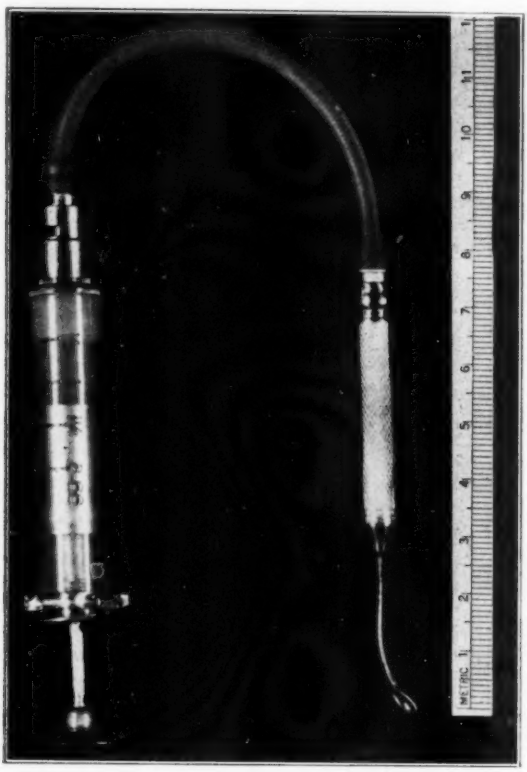

Fig. 3.—Suction instrument for cataract extraction devised by Thomas.[26]

length of firm rubber tubing and a special adapter with a convenient handle for manipulation of the suction cup. This instrument displaces a 5 mm. column of water 65 mm., an increase of 20 mm. over the original drawing power. The advantages of this instrument are its easy manipulation, adequate suction power and the self-controlled suction, which is automatically cut off when the cup is removed from the lens. The cup is inserted into the chamber and placed flat on

26. Thomas, C. I.: Suction Instrument for Cataract Extraction, Am. J. Ophth. **28**:317, 1945.

the lens capsule. Slight counterpressure just below the limbus often helps the operator in securing a firm grasp on the capsule. The assistant then applies the suction. The process of delivery is then carried out either by sliding or by tumbling the lens. Unless the lens presents itself in the wound and is easily dislocated, it has been found that tumbling enables the suction to be held more firmly than the sliding method. It should be emphasized that reapplication of the suction cup is not a hazard, and I have done this often with no complication in delivering the lens. An alert assistant enables immediate reapplication of suction to be carried out.

Motor-produced suction often has greater drawing power, but is not an essential and calls for the use of needless machinery. The greatest danger in this method is that it requires extra manual control to cut off the suction, since suction is not self controlled, as in the syringe. In motor suction, unless the cup is squarely on the lens, the suction may be disastrously applied. This untoward occurrence is easy when one is working at the lower periphery of the lens. However, the complication will not be encountered with the syringe, as the control of its drawing power depends on the proximity of the cup to the capsule itself.

TABLE 1.—*Data on 618 Attempted Intracapsular Extractions*

		Loss of Vitreous
Successful forceps extraction	450	25
Successful suction extraction	75	..
Ruptured capsule with forceps	87	..
Ruptured capsule with suction	..	..
Zonule too resistant and capsule purposely ruptured	6	..
Total	618	

Barraquer [17] made a point of subluxating the lens by rotation. This maneuver is an excellent one, but is not necessary in every case. If the zonular fibers are found to be especially elastic, either this maneuver can be tried or counterpressure can be exerted below and near the limbus to break these fibers. Rotation may not be necessary if the lens is dislocated readily.

COMMENT

In 75 of the 618 cases of intracapsular extraction of the lens studied, it was decided at operation to use the suction method. The character of the lens and the tonicity of the capsule were necessarily studied before the method to be used was decided on.

Table 1 shows the relative frequency of rupture of the capsule when the lens forceps is used, as compared with the incidence of rupture with the use of the suction instrument. The lens capsule forceps used were the Arruga, the Kirby and the Verhoeff type. It was found that

when the lens capsule ruptured it did so in almost any stage of the delivery, but most frequently before the lens had become completely dislocated. If the zonular fibers were found to be more resistant along either the nasal or the temporal side, and if one of these sites was the last to be dislocated, rather than continue the traction on the lens, one could "roll out" the lens on the side toward the resistant fibers, thereby lessening the chances of rupturing the capsule. Rupture of the capsule indicated that one of the following conditions existed: (1) The zonular fibers were more resistant than the capsule; (2) there were adhesions around the lens itself, holding it in the fossa, or (3) the area of traction was distributed over too small an area to bear the weight of the lens itself. The last factor was believed to be a frequent cause of failure in delivering the lens in the capsule, and its importance is apparent when one studies the traction lines shown in figure 2. In table 1, there is a conspicuous absence of cases in which the capsule was ruptured when the suction instrument was used. The percentage

TABLE 2.—*Conditions in Which The Suction Method Is Indicated*

Swollen, hypermature lens	30
Capsule too tight for application of forceps	28
Friable capsule	15
Exfoliation of lens capsule	2
Total	75

of cases in which vitreous was lost also bears comment. In all such cases of loss of vitreous the most likely cause was counterpressure. It should be kept in mind that this may not be a factor in extraction by suction.

Table 2 shows the types of cases in which the suction method is used to the greatest advantage. Again, I wish to emphasize that the operator should not decide on the type of operation to carry out before the chamber is opened and the lens examined. If any of the four conditions shown in table 2 exist, one should immediately proceed with extraction by suction. Cases with exfoliation of the lens capsule are included in this group, as with this condition intracapsular extraction is considered the safest method, and the surest way by which to carry out the extraction is with the suction instrument.

CONCLUSIONS AND SUMMARY

The method used for any cataract extraction should vary with the judgment of the surgeon.

The suction method of cataract extraction is used to its greatest advantage in cases in which the (1) lens is hypermature, (2) the cap-

sule is tense, (3) the capsule has exfoliated, (4) the lens must be dislocated before it is tumbled or slid out of the fossa, (5) the capsule is friable and will not stand any tension.

The advantages of the suction technic are (1) more even distribution of traction and (2) less counterpressure.

Pitfalls of the operation are discussed.

Contraindications to the use of the suction method are indicated.

An analysis of 618 cases of intracapsular extraction is presented to show the comparative frequencies of rupture of the capsule with use of the lens forceps and with the suction instrument.

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Clinical Notes

DISPENSER FOR ADHESIVE TAPE

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PHILADELPHIA

In carrying out routine hospital dressings in ophthalmic cases, there are few occasions which necessitate various lengths of adhesive tape. Cutting individual pieces of adhesive tape one at a time is a slow process, and they are not always of equal lengths. A dispenser was designed which enables the ophthalmic nurse to have ready for dressings strips of adhesive tape of similar lengths. This dispenser is made of plastic material and is 15 cm. wide and 60 cm. long.

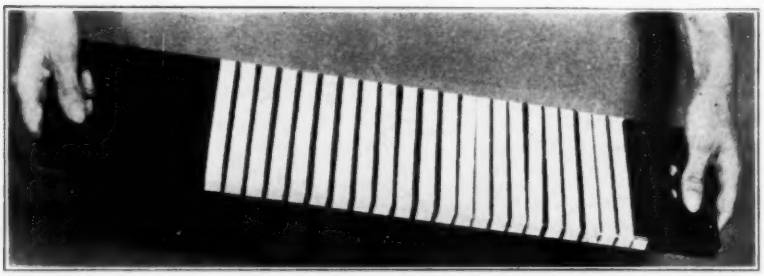

Fig. 1.—Side view of the adhesive tape dispenser with tape applied.

Two fingerholes, one at each end, enable the nurse to hold the dispenser easily either in the application or in the removal of the adhesive tape. Two small grooves run the entire length of the edge of the dispenser, allowing the bandage scissors to cut the tape easily. Small free tips of adhesive tape overlapping the grooved edges facilitate grasping it for removal. The adhesive tape does not lose any of its adherent qualities by contact with the plastic surface. This dispenser has been very satisfactory not only as a convenient and efficient carrier for adhesive tape, but as a time saver in ophthalmic nursing.

The dispenser was made by the John L. Van Arkel Company, Haddonfield, N. J.

Nineteenth and Lombard Streets.

* Resident, Department of Ophthalmology, Service of Dr. Edmund B. Spaeth, Graduate Hospital of the University of Pennsylvania.

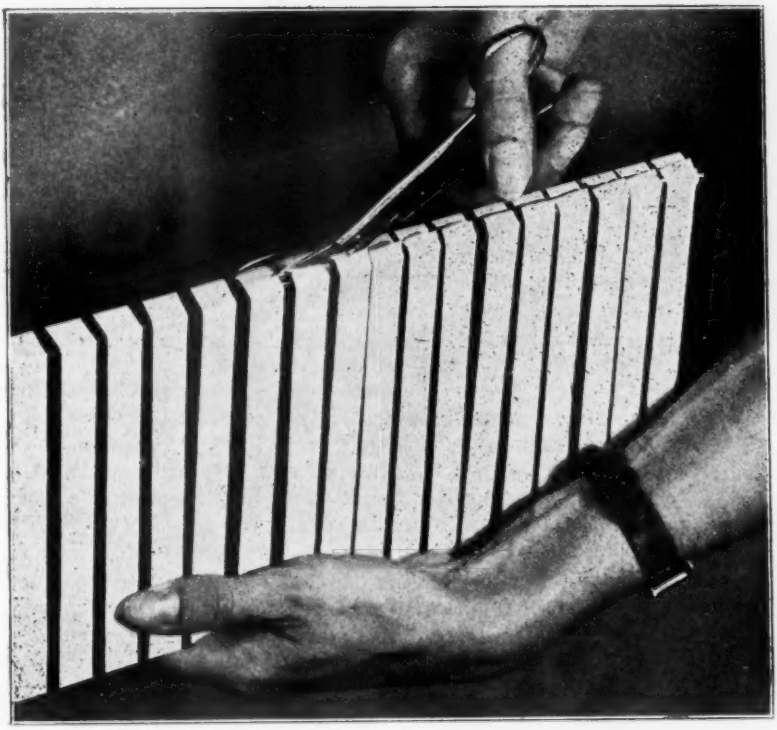

Fig. 2.—Cutting the adhesive tape with bandage scissors.

Correspondence

USE OF GLASS IRRIGATOR FOR ANTERIOR CHAMBER

To the Editor:—I still feel justified in using my blue-tipped glass irrigator, in spite of the fact that an accident has been reported in which a tip of the irrigator broke and remained in the anterior chamber.

I wish first to explain the function of my irrigator as it is designed. The blue tip certainly needs no explanation. The bulbous part of the irrigator serves two purposes. First, it prevents too forcible irrigation of the anterior chamber, for no matter how hard the rubber bulb is pressed there is a steady stream of fluid under uniform pressure. Second, the enlargement serves to prevent the introduction of minute particles of rubber into the eye which often come from the inside of the rubber bulb. These particles always present themselves in the small bowl before they can be introduced into the eye. I have seen 3 cases of particles of rubber in the anterior chamber. In 1 case definite harm was done, and in the others the position of the particles was confined to the anterior chamber, owing to the fact that there was a fine secondary membrane. The eyes showed no irritation due to the presence of these foreign bodies.

Probably a few words would be in order to explain how to irrigate the anterior chamber in the most efficient manner. In the first place, the irrigator for the anterior chamber which was made according to my specifications was never intended to be used as a spatula, either for the iris or for the wound, although on numerous occasions I have seen this maneuver performed. Ocular instruments are instruments of precision, and I do not think it possible to replace a well made spatula with an irrigator for the anterior chamber. As they serve distinctly different purposes, their construction must vary accordingly.

The following procedure, I think, is safe: Before the irrigator is to be used, I take a pledget of sterile cotton and wipe the irrigating tip from the under side. This accomplishes a number of purposes. If the tip is jagged, the defect can readily be seen by the contrast between the blue and the white. If it is cracked, the slight pressure exerted in this manner will readily indicate whether or not the instrument is safe to use.

In the actual irrigation, the irrigator can be moved from side to side, provided the operator's hand is not a fist. The irrigation should be started before the point of the irrigator is introduced into the wound; and it should also be borne in mind that it is often possible to wash out the anterior chamber successfully without introducing even the tip of the irrigator into the wound if the eye and the irrigating stream are in proper coaptation. For one not skilled in this operation, it is safer to irrigate from either angle of the wound, so that if the patient suddenly looks up the point of the apparatus will slip out of the wound and there will be no folding of the cornea.

Probably the most important part of the whole procedure is the direction of the stream of the irrigating solution. I have watched

many surgeons irrigate the anterior chamber, and some of them do not seem to realize that the proper way to remove material from the chamber is to direct the stream against the posterior surface of the cornea, not into the vitreous, and not at the material which is to be removed.

I am still of the opinion that, if used with caution, my irrigator is the best available though not perfect.

WILLIAM BROWN DOHERTY, M.D., New York.

150 West Fifty-Fifth Street.

CLOSURE OF CENTRAL RETINAL ARTERY AFTER GENERAL ANESTHESIA

To the Editor:—If any ophthalmologist has had occasion to see a case of closure of the central retinal artery, first recognized shortly after the patient came out of a general anesthesia, will he be so kind as to convey the details to me? Please note which eye was affected, type of anesthesia used, length of operation and its nature, whether or not the patient went into shock at the time of the operation and whether there was any evidence, such as corneal abrasion or ecchymosis of the lids, that the eye had been pressed on during the anesthesia.

I. GIVNER, M.D., New York.

108 East Sixty-Sixth Street (21).

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Foundation for Vision: *Terry Center for Visually Handicapped Children.*—The Foundation for Vision is the philanthropic organization which has carried on the projects of the late Dr. Theodore L. Terry. His investigation of retrolental fibroplasia has been continued at the Massachusetts Eye and Ear Infirmary by Dr. Everett Kinsey; the clinical studies have been made by Dr. Merrill F. King. A training course for the mothers of children afflicted with this type of blindness was arranged and given by Dr. Terry to a large group of mothers and children at the Perkins Institution, in Boston. Since his death, a few mothers have been instructed from time to time, but no organized work has been carried on. This course is to be reopened next summer at the Perkins Institute, under the auspices of the Foundation, as the Terry Center for Visually Handicapped Children. The details can be obtained from Dr. Gabriel Farrell, of the Perkins Institute, when arrangements are completed.

Ophthalmological Study Council.—The course in the basic subjects of ophthalmology will be given next summer, using the facilities of Westbrook Junior College in Portland, Maine. This is the fifth session of this course, which is under the supervision of the Ophthalmological Study Council, sponsored by the Foundation. Dr. Walter B. Lancaster, who organized and developed the previous courses, asked to be relieved of responsibility at the meeting of the Foundation in June and will be succeeded as director by Dr. Parker Heath, clinical professor of graduate ophthalmology at the Harvard Medical School. The arrangements for this course will be essentially the same as those for the previous sessions. The dates of the course will be published in the journals as soon as a decision has been reached.

American Board of Ophthalmology.—Candidates for the certificate of the American Board of Ophthalmology are accepted for examination on the evidence of a written qualifying test. These tests are held annually in various parts of the United States.

Registration is already closed for the next test, to be given in January 1949.

Applications are now being accepted for the 1950 written test. They will be considered in order of receipt until the quota is filled.

The practical examinations for acceptable candidates in 1949 will be held as follows: San Francisco, March 21 to 24; New York, June 11 to 15; St. Louis, October 15 to 19, and Boston, in December.

A supplementary list of diplomates from January 1948 to January 1949 will be sent without charge to all purchasers of the Board's "Directory." This supplementary material is arranged alphabetically and geographically. No biographic material is included.

Diplomates are urged to keep the office of the Board informed of all changes of address.

The officers for 1949 are: chairman, Dr. Frederick C. Cordes; vice chaiman, Dr. John H. Dunnington; secretary-treasurer, Dr. S. Judd Beach, and assistant secretary, Dr. Edwin B. Dunphy.

Communications should be addressed to the Executive Office, American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

German Ophthalmological Society.—The first meeting of the German Ophthalmological Society since 1938 has just been held in Heidelberg. As the hotels were occupied by the military personnel, the doctors were lodged in hospitals and in student barracks. The meetings were held in the University, under the direction of Professor Engelking, and lasted three days, the session beginning at 8 o'clock in the morning and continuing, with two hours' intermission, until 6 o'clock. A general dinner for participants took place on the first and second evenings; the food was good, as a German colleague in Montevideo had made a gift of butter, sugar, coffeè and tobacco. The scientific standard of the meeting was high; many good papers were presented and will be worth careful study when the *Transactions* appear. Among the foreign guests were J. D. Nordenson, of Stockholm, and D. G. Cogan, of Boston. Dr. Cogan gave the opening address.

The meetings were a proof of the wonderful way in which the German ophthalmologists are overcoming their great difficulties. Arrangements were discussed for the proper celebration of the Helmholtz centenary. The new president is Prof. K. Wessely, of Munich.

Estelle Doheny Eye Foundation Lecture in Ophthalmology.—Dr. Cecil S. O'Brien, professor of ophthalmology at the State University of Iowa College of Medicine, will deliver the Estelle Eye Foundation Lecture at the Los Angeles County Medical Association Building in Los Angeles on Nov. 8, 1948. His subject will be "The Surgical Treatment of Strabismus." The first of these annual lectures presented by the Estelle Doheny Eye Foundation in Los Angeles was delivered by Dr. Alan C. Woods, professor of ophthalmology at Johns Hopkins University and director of the Wilmer Ophthalmological Institute, on Dec. 17, 1947.

Seminar in Ophthalmology and Otolaryngology, University of Florida.—The Graduate School of Medicine of the University of Florida will hold a midwinter seminar in ophthalmology and otolaryngology at Miami Beach, Jan. 10 to 15, 1949. The lecturers in ophthalmology will be: Dr. John H. Dunnington, New York; Dr. Avery Prangen, Rochester, Minn.; Dr. Georgiana Theobald, Chicago; Dr. Derrick Vail, Chicago, and Dr. Alan C. Woods, Baltimore.

Early registration is advisable. The registration fee is $40. Application may be made to Dr. Walter T. Hotchkiss, 541 Lincoln Road, Miami Beach, Fla.

Annual deSchweinitz Lecture.—The eleventh annual deSchweinitz lecture, sponsored by the College of Physicians of Philadelphia, Section on Ophthalmology, will be delivered by Dr. William L. Benedict on November 18 on "Surgical Treatment of Tumors and Cysts of the Orbit."

UNIVERSITY NEWS

Refresher Course in Ophthalmology and Otolaryngology.—The University of Toronto Faculty of Medicine announces a refresher course in the combined subjects of practical ophthalmology and otolaryngology, to be given from Jan. 24 to Jan. 29, 1949.

The course will be so arranged that the operative procedures and bedside conferences of the one specialty will be held in the mornings and the didactic conferences or lectures in the afternoons. The reverse of this procedure in the other specialty will make it possible for each applicant to pick whatever subjects may be of interest to him.

Guest speakers will give lectures and clinics in both subjects of the course. The fee will be $60. The course will be given for a minimum of 10 students and a maximum of 20 students. Application should be made to the Medical Office, University of Toronto, and the closing date for application will be Nov. 30, 1948.

SOCIETY NEWS

Two New Ophthalmologic Societies in Rumania.—Notice has been received of the formation of two new ophthalmologic societies in Rumania. The first will be known as the Rumanian Society of Ophthalmology in Timisoara; president, Dr. Nicolas Blatt, and secretary, Dr. Nicolas Zolog. The second is the Rumanian Society for the Prevention of Blindness; president, Dr. Nicolas Blatt, and secretary, Dr. Virgil Popovici.

PERSONAL NEWS

Dr. Roscoe J. Kennedy Appointed Head of Department of Ophthalmology of the Cleveland Clinic.—Dr. Roscoe J. Kennedy has been appointed head of the department of ophthalmology at the Cleveland Clinic. After receiving his medical degree in 1931 at the State University of Iowa College of Medicine, Dr. Kennedy interned at the Harper Hospital, at Detroit, and served as resident at the Buffalo General Hospital and at the Wills Hospital, Philadelphia.

Dr. Kennedy came to the Cleveland Clinic in 1937 to complete a fellowship course of study and was appointed to the professional staff in 1938. In World War II he served for four years with the medical corps of the United States Navy in the Southwest Pacific, holding the rank of captain.

Dr. Kennedy was certified by the American Board of Ophthalmology in 1939 and has made various contributions to medical journals. He is secretary-treasurer of the Cleveland Ophthalmological Club and is also a member of the Cleveland Academy of Medicine, the American Medical Association and the American Academy of Ophthalmology and Oto-Laryngology. He was born at New Hampton, Iowa, and attended Notre Dame University.

The Eightieth Birthday Celebration of Sir John Herbert Parsons.—The September issue of the *British Journal of Ophthalmology* is a special number dedicated to Sir John Herbert Parsons on the occasion of his eightieth birthday. The number contains twenty-three articles, by friends from many countries, and three introductory expressions of appreciation, by Prof. E. D. Adrian, Prof. J. van der Hoeve and R. R. James. The members of the Faculty of Ophthalmology and the Ophthalmological

Society of the United Kingdom presented Sir John Herbert Parsons with a portrait in oil, painted by John Gorlay, in honor of his eightieth birthday. The presentation took place at the Royal College of Surgeons on Sept. 3, 1948. The presentation speech was made by Sir Stewart Duke-Elder; the portrait was then unveiled by Lady Duke-Elder, and Sir John made a brief reply.

Dr. Arthur J. Bedell Lectures at Meeting of Pan-Pacific Surgical Association.—Dr. Arthur J. Bedell, of 344 State Street, Albany, N. Y., attended the meeting of the Pan-Pacific Surgical Association in Honolulu, Hawaii, August 30 to September 13. He gave a series of three lectures before the society.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Congenital Anomalies

OPHTHALMOLOGIC IMPORTANCE OF ANOMALIES OF THE SELLA TURCICA. R. BAROLOZZI, Arch. Soc. oftal. hispano-am. **7:** 671 (July) 1947.

While making anatomic studies of a number of skulls, the author observed an anomaly of the sella turcica which may have a bearing on the syndrome of glaucoma without hypertension. This anomaly consisted of fusion of the anterior, middle and posterior clinoid processes by means of a bony bridge. This observation is not new, but no importance has been attached to it. It is not necessarily a process of old age. The fusion of the anterior and the middle clinoid process gives rise to the formation of a circular orifice (the carotid foramen), through which the terminal portion of the internal carotid artery passes. The anomaly has nothing to do with displacement of the optic nerve. It could, however, influence the course of the internal carotid artery, which in passing through the anomalous carotid foramen could be pushed against the optic nerve, forming a closer than normal contact.

This anomaly would have practical interest, since it could explain cases of atrophy of the optic nerve and chiasmic lesions in which no calcification of the vessel is apparent.

H. F. CARRASQUILLO.

Cornea and Sclera

THE PRESERVATION OF CORNEAL TISSUE BY FREEZING AND DEHYDRATION. H. M. KATZIN, Am. J. Ophth. **30:** 1128 (Sept.) 1947.

Katzin attempted to preserve rabbit corneas for transplantation by rapid freezing at the temperature of liquid nitrogen and dehydrating *in vacuo* at — 40 C. These grafts took and healed in place but did not remain clear, despite various modifications in technic.

W. S. REESE.

LOCAL SULPHONAMIDE THERAPY OF DENDRITIC ULCER. H. L. HUGHES, Brit. J. Ophth. **32:** 43 (Jan.) 1948.

A series of 16 cases of dendritic ulcer of the cornea treated locally with sulfonamide compounds is presented. The mode of treatment was to instil 6 per cent "albucid" (azosulfamide) ointment three times a day and paint the entire corneal surface once daily with 30 per cent solution of azosulfamide.

As Sorsby pointed out, the good results obtained with sulfonamide therapy raise the question whether dendritic ulcer is to be regarded as a herpetic virus infection. It is possible that the high concentration reached with local treatment is effective against the virus.

W. ZENTMAYER.

CORNEAL DYSTROPHY ASSOCIATED WITH IRITIS AND ARTHRITIS. G. H. B. BLACK, Clin. Rep. Adelaide Childrens Hosp. **1:** 70 (Nov.) 1947.

Black reports a case of a band-shaped area of corneal dystrophy and iritis affecting both eyes in a child aged 10 years. Definite bony changes were present in the proximal phalanx of the thumb, and there was subacute arthritis of the left knee joint.

W. ZENTMAYER.

TREATMENT OF THE SERPIGINOUS ULCER WITH PENICILLIN. P. MATA, Arch. Soc. oftal. hispano-am. **7:** 641 (July) 1947.

The author treated 30 patients with serpiginous ulcer of the cornea with penicillin. To the conclusions given by Keefer in 1943 on the findings of the Committee on Chemotherapeutic Agents, based on the reports of more than twenty groups of investigators which made their studies in the United States, Mata adds that the local application of penicillin as used in treatment of serpiginous ulcer has the great advantages of acting directly on the infectious agents, that its antibiotic action is not influenced by the presence of blood, pus, exudates or autolytic products and that it must be administered periodically and continuously, using the maximum concentrations if necessary without fear of any deleterious effect on the tissues.

In reporting the results obtained with the treatment, he divided his series of cases in four groups: (1) 3 cases, in which treatment began with sulfonamide drugs, with no improvement, followed by administration of penicillin; (2) 9 cases of moderately severe lesions; (3) 9 cases of severe lesions, and (4) 9 cases of advanced lesions with complications. In groups 1, 2 and 3 the results of treatment with respect to cure were excellent. In group 4, in spite of the advanced stage of the ulcers and the existing complications, the results were satisfactory.

The penicillin used was of the purest quality. It was administered by iontophoresis, using a Wertz electrode and solutions of high concentration (from 2,500 to 6,000 units per cubic centimeter), by subconjunctival injections of maximum doses of 5,000 units and by continuous instillations of solutions of up to 10,000 units per cubic centimeter.

Ascorbic acid was also given intravenously in many of the cases.

H. F. CARRASQUILLO.

General Diseases

LYMPHOGRANULOMA VENEREUM. H. G. SCHEIE, A. S. CRANDALL and W. HENIE, J. A. M. A. **135:** 333 (Oct. 11) 1947.

In the 5 cases described the corneal lesions were identical. In the 1 case in which the lesion was followed from its onset, the condition began as ordinary keratoconjunctivitis localized to the upper portion of the limbus. Corneal infiltrates appeared within the upper limbus, and as they increased in number they became confluent, forming an arc involving one-third to one-half the circumference of the cornea. The entire thickness of the cornea became involved, but the process gradually became superficial centrally over its advancing border. A dense superficial vascularization from the limbus covered the infiltrate so profusely that it elevated the surface like an epaulet. A milky iridocyclitis was present.

Evidence supporting the diagnosis of lymphogranuloma venereum consisted in the following observations: (*a*) a positive Frei reaction in all cases; (*b*) involvement of inguinal lymph nodes, active in 1 case and healed in 3 cases; (*c*) a strongly positive complement fixation reaction in 1 case, and (*d*) in the corneal lesion of the same case, inclu sion bodies compatible with lymphogranuloma venereum as shown by biopsy. Although the prognosis is serious, sulfathiazole or sulfadiazine should be given in full therapeutic doses for not less than three weeks.

W. ZENTMAYER.

"MAPHARSEN" IN REITER'S DISEASE. E. N. KHOURY, J. Urol. **58**: 221 (Oct.) 1947.

Khoury points out that Reiter's syndrome has a basic triad of nongonococcic urethritis, conjunctivitis and arthritis. The general belief is that it is one of the many virus infections. In cases reported in the literature, the course was generally protracted, but this is not an invariable observation, inasmuch as in at least 1 of the 2 cases reported here the disease was benign and cleared in a comparatively short time. In the second case the condition may be classed as moderately severe. However, it did cause protracted disability. Large doses of oxophenarsine hydrochloride U. S. P. ("mapharsen"), which were started four months after onset of the urethritis, caused such a rapid and dramatic response that the possibility of a coincidental spontaneous regression cannot be rationally entertained. The author thinks that in future cases of this syndrome this form of therapy should have a trial. "Mapharsen" was given in two injections a week for three weeks, then one injection a week for four weeks. The dose was 0.06 Gm., administered intravenously.

J. A. M. A. (W. ZENTMAYER.)

RETINAL COMPLICATIONS OF DIABETES MELLITUS. J. L. R. CANDELA, Arch. Soc. oftal. hispano-am. **7**: 851 (Sept.) 1947.

Clinically, the presence of diabetic retinopathy cannot be attributed to the hyperglycemia of diabetes. It is a well established fact, however, that diabetic patients, more particularly those presenting retinal complications, have a high capillary fragility. The author, following the technic of Göthlin, found in these patients a moderately high petechial index. He also found in dogs with alloxanic diabetes disturbances in the plasma proteins with no relation to the lipids and cholesterol contents, as described by other observers, but coinciding with the presence of the retinal lesions of the disease.

Experimentally, the alterations in the plasma proteins are constant in the diabetes of pancreatic origin, and in 80 to 100 per cent of the cases of the alloxanic type.

Candela has prepared a pancreatic extract the administration of which would bring to normal the altered plasma proteins much sooner and more completely than the establishment of any type of diet. The retinal lesions present are also considerably improved. Besides this, by the use of the extract, the complementary activity of the plasma is restored to normal, and the elimination of nitrogen in the urine is also decreased.

H. F. CARRASQUILLO.

Glaucoma

CYCLODIALYSIS, MULTIPLE OR SINGLE, WITH AIR INJECTION. O. BARKAN, Am. J. Ophth. **30:** 1063 (Sept.) 1947.

Barkan describes his method of cyclodialysis, multiple or single, combined with injection of air. The latter procedure is designed to control hemorrhage, widen the cyclodialysis cleft and make it visible and, by restoring and deepening the anterior chamber, make possible multiple cyclodialysis. The results reported are based on operations performed on 83 eyes.

W. S. REESE.

THE SIGNIFICANCE OF THE BASE PRESSURE IN PRIMARY GLAUCOMA. A. B. REESE, Am. J. Ophth. **31:** 25 (Jan.) 1948.

The importance of study of the base rather than the peak pressures in glaucoma, particularly the long range trend, is emphasized. Operative measures are based on these studies, together with the type of glaucoma.

In glaucomatous eyes the height to which the pressure rises is referred to as the "peak pressure," and the depth to which the pressure descends, as the "base pressure." Any sustained elevation of the base pressure indicates permanent damage to the filtration angle. The more advanced the glaucoma, the more nearly the base pressure approaches the peak pressure, so that in absolute glaucoma they tend to merge.

W. ZENTMAYER.

Injuries

OBSERVATIONS ON 300 CONSECUTIVE CASES OF OCULAR WAR INJURIES. J. G. BELLOWS, Am. J. Ophth. **30:** 309 (March) 1947.

The article does not lend itself well to abstracting. The cases are considered under (1) injuries caused by air blasts or burns; (2) concussion waves reaching the eye through the tissues, caused by direct impact on an adjacent structure or, less frequently, at a more distant point, and (3) direct impact of a missile on the eyeball.

W. S. REESE.

OCULAR LESIONS FOLLOWING THE ATOMIC BOMBING OF HIROSHIMA AND NAGASAKI. J. J. FLICK, Am. J. Ophth. **31:** 137 (Feb.) 1948.

Flick states that the transient nature of the condition and the chronologically short period over which the studies were made do not permit definite conclusions. It seems safe, however, to conclude that the ocular lesions here described are directly related to the deficiency in blood elements, and in no way directly related to the action of radiant energy on the eye. The lesions were observed to disappear in persons recovering from the hematopoietic depression, with no residual damage to the eye. It is believed that this healing occurred in all patients who survived the irradiation and that no permanent residual damage resulted from the retinal lesions. As to the vexatious question of radiation damage to the lens, time alone will tell.

W. S. REESE.

Lens

MICROPUNCTURE OF HYPERMATURE CATARACTS WHOSE CAPSULES CANNOT BE GRASPED WITH THE CAPSULE FORCEPS. J. SÉDAN and S. SÉDAN BAUBY, Ophthalmologica **114:** 65 (Aug.) 1947.

In a number of hypermature cataracts, it is impossible to grasp the capsule with the ordinary capsule forceps in performing an intracapsular extraction. The authors find that if a knife needle is inserted through the peripheral iridotomy wound into the lens, sufficient fluid lens material comes out of the puncture wound to enable one to grasp the lens capsule with the capsule forceps and extract the lens intracapsularly, in the usual manner. They also cite a somewhat similar variation of this precedure, described earlier by a colleague, Charles Thomas, of Nancy.

F. H. ADLER.

IRIDODIALYSIS AFTER EXTRACTION OF CATARACT CURED BY ELECTROCOAGULATION DIATHERMY. K. SAFAR, Ophthalmologica **114:** 77 (Aug.) 1947.

In cataract extraction in which the iris has been torn from its roots, giving rise to iridodialysis, the root of the iris may be brought forward by means of a small hook or fine iris forceps through a small keratome incision at the limbus. It is pulled into the wound and fastened there by means of gentle electrocoagulation. This method is simple and effective, and the scar formed holds the iris in place. It may be employed with success in cases of aphakia, as well as in eyes with lenses in which the iridodialysis is traumatic.

F. H. ADLER.

Lids

CORRECTION OF SOME FORMS OF ACQUIRED PTOSIS. EDMUND B. SPAETH, Plast. & Reconstruct. Surg. **2:** 37, 1947.

The types of blepharoptosis are classified, and recommendations are made as to the operation of choice for the individual type. The classification of congenital blepharoptosis is based mainly on whether the superior rectus muscle or the third and sixth nerves are involved. Acquired blepharoptosis is classified chiefly on a basis of nerve or tissue damage. Three types of surgical treatment are especially recommended: (1) use of bands for support, according to the method of Hess; (2) utilization of fibers of the orbicularis, as devised by Reese, and (3) resection of the levator muscle and the tarsus, employing the Blascovics technic.

LOREN P. GUY.

THE OCULOPALPEBRAL SYNDROME OF THE PREMENOPAUSE. A. KOUTSEFF, Bull. Soc. d'opht. de Paris, November-December 1946, p. 92.

The author reports 2 observations in which he believes that the role of the pituitary gland may be of importance in the control of edema of the lids previous to menstruation. Estrogen is thought to be the element which is basically responsible for the syndrome.

L. L. MAYER.

Methods of Examination

FACTORS IN DIAGNOSIS OF ANISEIKONIA AND PAIRED MADDOX-ROD TESTS. P. W. MILES, Am. J. Ophth. **30:** 885 (July) 1947.

Miles outlines his views on factors in the diagnosis of aniseikonia, tests for stereoscopic acuity and binocular methods of noncycloplegic refraction. He describes a method of measuring aniseikonia with paired Maddox rods.

W. S. REESE.

ROENTGENOSCOPIC METHOD APPLICABLE TO THE DIAGNOSIS AND LOCALIZATION OF INTRAOCULAR FOREIGN BODIES. M. ESTEBAN, Arch. Soc. oftal. hispano-am. **7:** 1084 (Nov.) 1947.

By making use of x-ray appliances which have permitted the odontologist to make roentgenoscopic studies of the alveolar processes of the teeth, Esteban has succeeded in making fluoroscopic studies of the eye and determining the presence and localization of intraocular foreign bodies. He used for his observations a Ritter dental x-ray unit. The method of examination is fully described, and the advantages of the roentgenoscopic study over the examination of the film are enumerated.

H. F. CARRASQUILLO.

PERIMETRIC LOCALIZATION OF LESIONS OF THE FUNDUS. A. VAZQUEZ BARRIERE, Arq. brasil. de oftal. **10:** 1, 1947.

By ophthalmoscopic localization is implied the determination of the situation of lesions in the fundus with relation to fixed points of reference, such as the disk, in the internal part of the eye, and the sclerocorneal limbus or the optic nerve, in the external part. The procedures for localization of retinal tears can be divided into two groups: (*a*) those carried out before operation, and (*b*) those carried out during the operation. Only the first group is considered. A historical summary of the methods of localization is presented. The author has made several modifications in the technic, and these are presented in great detail.

M. E. ALVARO.

Neurology

COMPLETE REMOVAL OF CRANIOPHARYNGIOMA WITH RECOVERY FROM BLINDNESS. W. T. GRANT, Bull. Los Angeles Neurol. Soc. **12:** 53 (March) 1947.

Grant was unable to find the report of a case of total removal of a suprasellar cyst or craniopharyngioma. He presents such a case. A boy aged 2 years was apparently well until he fell on his forehead. Failing vision began in four days, and the boy was totally blind in twelve days. At operation, four weeks and two days after the onset of blindness, a large suprasellar cystic tumor was collapsed by aspiration and removed intact. It was necessary to divide the right optic nerve to accomplish this. A narrow stalk connected the base of the tumor with the pituitary fossa. Response of the left pupil to light was present two days after operation, and the patient was able to see on the seventh day. He had useful vision at the time of the report. The history

suggested strongly that trauma was a factor in causing blindness. Cushing observed that the history of preceding trauma was surprisingly common as an apparent factor in stirring suprasellar cysts into activity. The absence of blood pigment in the wall of the cyst and of red blood cells in the cyst fluid would be against the contention that an intracystic hemorrhage had occurred at the time of the blow on the head. When the patient fell on the right side of his forehead, one would expect that the tumor would be thrust forward temporarily at the moment of the impact. This could hardly damage the optic nerves without causing visual impairment at once. But it could tear arachnoidal or other bands of tissue that were constricting the tumor. This would allow the lesion to expand gradually after the injury and would seem to fit the train of events in the present case.

W. ZENTMAYER.

HYSTERICAL AMAUROSIS. EDSON PINHO, Arq. brasil. de oftal. **10:** 16, 1947.

The case is presented of a 19 year old girl who became suddenly blind in the right eye and had vision limited to counting fingers at 1 meter in the left eye. The globe and adnexa were normal. The personal history was one of shock after the imprisonment of her husband. Psychiatric treatment was carried out, mock operations being performed by her ophthalmologist, who explained the "treatment" in detail; but results were poor. Four months later she was examined again. Visual acuity was 1/10 at 5 meters in each eye. With her husband's return home, her vision became normal.

M. E. ALVARO.

CLINICAL PICTURE OF RETROBULBAR NEURITIS IN CASES OF INTRACRANIAL TUMORS. S. LARSSON and B. NORD, Nord. med. (Hygiea) **34:** 1059-1066 (May 2) 1947.

Larsson and Nord warn that in cases of tumor in the anterior or middle fossa reduced vision and central scotoma, with or without papilledema or atrophy of the optic nerve, constitute an early symptom, the diagnostic value of which is frequently not recognized. The symptom is often attributed to sclerosis disseminata, and surgical intervention is thus delayed. Especially in cases with a protracted course, encephalographic studies are indicated. Eight personal cases, namely, 2 cases of meningioma of the olfactory groove, 2 cases of suprasellar meningioma, 1 case of meningioma originating in the lesser wing of the sphenoid, 1 case of adenoma of the hypophysis, 1 case of tumor of the hypophysial duct and 1 case of subfrontal meningioma, are described in detail. Diagnostic difficulties were presented in all, and retrobulbar neuritis was always prominent. Spontaneous improvement in vision suggested the erroneous diagnosis of sclerosis disseminata in the first 4 cases. In 1 case the ocular symptoms were ascribed to anemia; in 1, to possible cerebral trauma; in 1, to arteriosclerosis, and in only 1 case was the diagnosis of cerebral tumor made without preceding misconception.

J. A. M. A. (W. ZENTMAYER).

Ocular Muscles

EFFECTS OF PRACTICE AND THE CONSISTENCY OF REPEATED MEASUREMENTS OF ACCOMMODATION AND VERGENCE. J. BROZEK, E. SIMONSON, W. J. BUSHARD and J. H. PETERSON, Am. J. Ophth. **31:** 191 (Feb.) 1948.

Brozek, Simonson, Bushard and Peterson summarize their findings as follows:

1. Measurements of ocular accommodation and vergence were made on 6 subjects under standard conditions.

2. The measurements were repeated at intervals of two to three days in a series of eighteen testing sessions.

3. Two preliminary trials were sufficient in the majority of the routine ophthalmic tests used to stabilize the scores at a plateau.

4. The measurements provide reasonably constant characteristics of the individual subjects.

W. S. REESE.

PARALYSIS OF DIVERGENCE. A. U. ZAVALA JR., Arch. Soc. oftal. hispano-am. **7:** 890 (Sept.) 1947.

The author discusses fully the controversial question of the existence of a separate innervation for the act of divergence. Supporting the view that such innervation is present, he makes the following statements: (1) It is hard to believe that of the fusional movements only convergence should lack an antagonistic action; (2) the divergence movements not only are necessary to bring the visual axes from the position of convergence to that of parallelism, but also must be present to overcome an esophoria; (3) the tests used to determine the fusional movements show the presence of active movements of divergence; (4) it is erroneous to think that the limit of divergence corresponds to the position of rest brought about by complete relaxation of the convergence.

A typical case of paralysis of convergence usually has the following characteristics: (1) Onset is sudden and there is constant homonymous diplopia for objects farther than 25 or 50 cm.; (2) the angle of deviation is usually small and at times unnoticeable, does not change when the eyes are directed laterally but does change when the eyes are moved up and down; (3) the field of fixation is normal; (4) base-out prisms will give to the patient normal binocular vision; (5) the angle of deviation is constant.

The author describes his personal observation of a case.

H. F. CARRASQUILLO.

Operations

SURGICAL TECHNIC IN OBTAINING FINE SCARS. C. R. STRAATSMA, Plast. & Reconstruct. Surg. **2:** 21, 1947.

Six long-established principles for good union of tissue with a minimum of scar formation are reiterated. 1. A right angle incision is used; a bevel is avoided. 2. Tension lines or natural folds are followed. 3. Relaxation of the edges is insured; avoidance of tension is essential. 4. Fine external sutures are used. Silk sutures are generally preferred.

5. Skin sutures are removed early. 6. Skin edges are supported. This is done by use of adhesive bands or strips of collodion for at least four weeks after operation.

Keloids present a problem. Radium and roentgen therapy are helpful in prevention and removal. Excision to within ⅛ inch (3 mm.) of the external border of the keloid with suture of the edges together except where there is unavoidable tension is the surgical method of removal.

LOREN P. GUY.

Pharmacology

DISTRIBUTION OF PENICILLIN IN THE EYE AFTER SUBCONJUNCTIVAL INJECTION. A. SORSBY and J. UNGAR, Brit. J. Ophth. **51:** 517 (Sept.) 1947.

Sorsby and Ungar found experimentally that substantial concentrations of penicillin in the ocular tissues, many times the usual therapeutic level, can be obtained by the subconjunctival injection of crystalline penicillin in a dose of 50,000 units. Adequate levels persist for six hours. The concentrations are distinctly higher if epinephrine hydrochloride (1 : 1,000) is used as the solvent for the penicillin. Observations on 5 human eyes support the results obtained experimentally.

W. ZENTMAYER.

INFLUENCE OF COFFEE ON THE NORMAL OCULAR TENSION. CYRO DE REZENDE, Arch. de oftal. de Buenos Aires **23:** 45 (Jan.-March) 1947.

After discussing modern knowledge of the chemical composition, pharmacodynamic action and effects which coffee exerts on the organism, the author reviews the studies which deal with the effect of coffee on ocular tonus.

In this preliminary study, he presents the results of normal ocular tension under the effect of a coffee infusion with a concentration of 100 grains (16.5 Gm.) of powder in 150 Gm. of water.

The results obtained on 100 subjects were as follows: an increase in 43.5 per cent, a decrease in 27 per cent and no change in 29 per cent.

M. E. ALVARO.

Physiology

DURATION OF BRIGHTNESS OF POSITIVE AFTER-IMAGES. M. PANNEVIS, Ophthalmologica **113:** 280 (May) 1947.

An intensive after-image is projected onto a screen, the brightness of which can be varied and registered. The brightness of the after-image is characterized by the intensity of the illumination of the screen which gives the same sensation of light as the after-image which is projected onto it (change from positive to negative after-image). The decrease in brightness follows the potential equation $H = t^a\ e^b$, in which a, b and e are constants and t stands for time. These processes are slower than the initial physical processes and, as far as can be judged, are different from and quicker than the higher nervous reactions. In this case, each successive reaction of this series takes place at a slower rate than the preceding one. Peripheral after-images, following the same light stimulus, are less intensive and fade out quicker. In the area

of a central scotoma, the after-image can be entirely absent. On the return of vision, it appears first peripherally and then centrally.

F. H. ADLER.

Refraction and Accommodation

CONTACT LENSES. I. MANN, Brit. J. Ophth. **31:** 565 (Sept.) 1947.

This paper is the presidential address delivered before the Contact Lens Society.

The problems of the contact lens fall under two types: those of optics and those of haptics. Much remains to be done if an optical accuracy comparable to that obtained with spectacle lenses is to be attained. The problem of the introduction of prisms, cylinders and bifocal glasses into contact lenses has still to be mastered. The author's interest in the subject is purely clinical. In a follow-up study of 100 patients, some of the problems have been formulated. Of the 100 patients, 61 were myopic; of these, 11 only wore a correction of — 5.00 D. sph. or under, the rest having very high corrections, up to — 22.00 D. Eleven had conical corneas, and the rest presented various disabilities, including high hypermetropia, binocular aphakia, corneal scars and dystrophies. The patients wore a single lens only for monocular aphakia. Of 84 patients who replied to the question whether they inserted their lenses dry or used a solution, 49 stated that they inserted them dry. Eight could not wear a lens at all. One, with sixteen to eighteen hours of wear every day, always put his lens in his mouth before inserting it; others used a boric acid solution, tap water or distilled water, with varying periods of tolerance. Various reasons were given for intolerance. For many, the corneal veil caused the most trouble. Other interesting data are given in the article.

W. ZENTMAYER.

Retina and Optic Nerve

DICUMAROL AND RUTIN IN RETINAL VASCULAR DISORDERS. A. L. MACLEAN and C. E. BRAMBEL, Am. J. Ophth. **30:** 1093 (Sept.) 1947.

MacLean and Brambel conclude that sufficiently significant results have been obtained to warrant further clinical evaluation of dicumarol and rutin. They found dicumarol efficacious in treatment of occlusion of the central and tributary retinal arteries and of diabetic, degenerative and central serous retinopathies. Rutin was of benefit in cases of recurrent retinal and vitreous hemorrhage.

W. S. REESE.

RETINAL ARTERY OCCLUSION. I. C. MICHAELSON, Brit. J. Ophth. **33:** 111 (Feb.) 1948.

A woman aged 41 had had defective vision in the left eye for six days. Vision was limited to counting fingers at 1 meter. Ophthalmoscopic examination showed occlusion of the macular branch of the inferior temporal artery. Fifteen minutes after the retrobulbar injection of acetylcholine there was notable diminution of the retinal opacity, which was confined almost entirely to the area between the affected artery and the macular vein; further clearing occurred, so that seven days later a faint sheathing was first noticed at the site of the spasm. Vision

improved to 6/24, the lower part of the letters being seen. The upper half of the field was lost to 2 mm. white test objects at 1,000 mm.

W. ZENTMAYER.

TREATMENT OF RETINAL DETACHMENT. H. ARRUGA, Arch. Soc. oftal. hispano-am. **7:** 1001 (Oct.) 1947.

Following Gonin's report of his operation for retinal detachment, the average rate for cure was about 25 per cent of cases in which his method was used. However, with improvements in the technic, the percentage of recoveries has been gradually increased to the present rate of 70 or 80 per cent of unselected cases. For the last six or eight years this rate has not been improved.

Arruga states that of the 20 or 30 per cent of cases in which operation does not result in improvement, poor results are expected beforehand, for obvious reasons, in approximately one-half, but the other half are cases in which there was confidence in good results, since in similar ones operation had previously been followed with success. In these cases good results were not obtained because of anomalous development of the curative process.

The cases in which the operation was not successful are analyzed under the following heads: (1) detachments anatomicopathologically benign with unfavorable evolution; (2) detachments beginning at the macula; (3) detachments located inferiorly.

The conditions which prevailed to produce poor results after the operation are described.

H. F. CARRASQUILLO.

THE CHANGES OF THE OPTIC NERVE IN NEURO-INFECTIONS. F. YUSEFOVA and Z. GORILOVSKAYA, Vestnik oftal. **26:** 11, 1947.

In the Kiev Psychoneurological Institute, during 1945 and 1946, 36 to 40 per cent of the patients admitted had neuroinfections. An analysis of the cases of 80 patients with changes in the optic nerve is given in this paper. There were 35 patients from 10 to 20, 27 patients from 20 to 40 and 18 patients over 40 years of age. Forty patients had encephalitis; 12, encephalomyelitis; 13, meningoencephalitis, and 15, disseminated lesions of the nervous system and polyneuritis. The changes in the optic nerve varied from mild signs, such as engorgement of the veins and hyperemia of the disk (microsymptoms), to marked neuritis, choked disks and pallor of the disk, resulting in optic atrophy. Atrophy of the optic nerve was observed in 26 of 40 patients with encephalitis. Of patients with encephalomyelitis, mild changes of the optic nerve were seen in about one-half; in some, pallor of the disks was observed. The most serious changes in the form of choked disks and optic nerve atrophy (in 12 of 13 patients) were seen in patients with meningoencephalitis.

In patients with microsymptoms, whose vision and visual fields were normal, the blindspot was enlarged and oblong. This, according to Samoilov, is related to retinal edema with accumulation of serum in the perivascular lymph space of the central retinal vein. The enlargement of the blindspot is an early manifestation of the involvement of the optic disk.

O. SITCHEVSKA.

Tumors

CYSTIC MALIGNANT MELANOMA OF THE UVEAL TRACT. R. E. KENNEDY, Am. J. Ophth. **31:** 159 (Feb.) 1948.

Kennedy reports a case and concludes that cystic malignant melanoma may present a diagnostic problem when it occurs in the posterior chamber, where its differentiation from a benign uveal cyst is difficult. The determination of translucency and the diagnostic puncture may differentiate a solid and a cystic mass in the posterior chamber, but cannot differentiate a benign and a malignant cystic mass. Thus, these diagnostic procedures are unreliable. When accessible, iridectomy and microscopic examination should be used in diagnosis of such lesions when their nature is in doubt.

Large cystic spaces in malignant melanomas arise from the growth of small focal areas of tumor necrosis, which are the result of inadequate nutrition. The cystic manifestation is present in about 8 per cent of all malignant melanomas of the uvea, has no predilection for the site in the uvea or the cell type and has no apparent effect on the prognosis of malignant melanomas.

W. S. REESE.

TWO UNUSUAL SCLERO-CORNEAL NEOPLASMS. A. LOEWENSTEIN and J. FOSTER, Brit. J. Ophth. **32:** 1 (Jan.) 1948.

In a boy aged 15 years a tumor resembling a phlycten developed at the limbus of the cornea at 11 o'clock. The growth doubled in size in five weeks and when removed was 3.5 mm. in diameter. A detailed histologic description of the enucleated eye is presented. The following summary is given: A hard, painless limbal tumor of rapid growth, infiltrating both the cornea and the sclera, with dilated vessels in the overlying conjunctiva, was removed locally. Histologically, this tumor was a spindle cell sarcoma of mature type, unequal cell distribution and a high degree of vascularization, with giant cell formations in the vessel walls. Abundant large mast cells with a big, round nucleus were present. Metachromatic granules filled the cytoplasm of certain fibroblasts and were also seen free in tissues.

As the clinical progress was more rapid than the histologic picture would suggest, the eye was excised. With the slit lamp, a milky film was observed covering the periphery of the retina and continued forward over the ciliary processes. There were no signs of uveitis.

The second case was that of a woman aged 65. The clinical history was obscure. The right eye had been blind about fifteen years. The growth appeared ten years later. On the lower two thirds of the cornea was a cauliflower-like growth, of firm consistency. The eye was enucleated. The neoplasm was a fibroma, containing areas of calcareous and myxomatous degeneration arising from a degenerative pannus. Both the growth and the pannus tissue contained mast cells.

It is suggested that the agent producing the metaplasia may be a virus similar to the Shope fibromatous type in wild rabbits.

W. ZENTMAYER.

FIBROMA OF THE ORBIT. A. GARCIA MIRANDA, Ophthalmologica **113:** 149 (March) 1947.

The author reports a rare case of fibroma of the orbit and its removal by means of the Krönlein operation. The histopathologic picture is described.

F. H. ADLER.

TRUE GLIOMA OF THE RETINA. A. HUGGERT and G. T. HULTQUIST, Ophthalmologica **113:** 193 (April) 1947.

Until now, only 2 cases of true retinal glioma have been reported in the literature: 1 by Dejean (*Arch. d'ophth.* **51:** 257, 1934) and the other by McLean (ARCH. OPHTH. **18:** 255 [Aug.] 1937). The authors report a case in which they consider one of true glioma or oligodendroglioma in a man of 77 who had had an intraocular tumor for twenty years, which finally necessitated removal of the eye. The tumor was rich in cells and for the most part was made up of medium or small cells, with nuclei fairly rich in chromatin and with varying amounts of cytoplasm. In some places, the cytoplasm was scanty and somewhat dark; but on the whole it was fairly abundant, light and vacuolated, with a darker-staining outer zone. Because of this arrangement, the groups of cells presented a honeycombed appearance. With silver impregnation by the Penfield modification of the method for oligodendroglia, a fair number of argentophilic cell elements with one or more short, sometimes dendritic, processes were observed. No distinct astrocytic elements were observed, and there was no filament formation in Holzer preparations. Around the blood vessels there were tumor cells, presenting a pseudorosette arrangement. In its abundance of mitotic figures and extensive areas of necrosis, the tumor diverged somewhat from the general picture typical of oligodendroglioma; but since these features have also been previously observed in brain tumors of this type, the authors believe that this does not militate against the diagnosis of the tumor in their patient.

F. H. ADLER.

UNUSUAL TUMORS OF THE LACRIMAL CARUNCLE. M. RADNOT, Ophthalmologica **113:** 270 (May) 1947.

Two tumors of the lacrimal caruncle are described. The first occurred in a man aged 69. Histologic examination revealed a cystic tumor, which the author describes as an "oncolytic cyst" derived from an accessory tear gland. The second case occurred in a man aged 67 with a clinical diagnosis of cornu cutaneum. Histologic examination showed a giant cell sarcoma, similar to a perithelioma.

F. H. ADLER.

Uvea

CONCERNING CHOROIDITIS PROLIFERANS. CHEN YEN, Am. J. Ophth. **31:** 207 (Feb.) 1948.

Yen concludes that choroiditis proliferans seems to be the end result of an exudative, inflammatory detachment of the retina. A hemorrhagic origin can be ruled out almost with certainty. The condition presents a well defined clinical picture.

W. S. REESE.

AN UNUSUAL CASE OF SYMMETRICAL, BILATERAL, NON-TRAUMATIC IRIS PROLAPSE. M. L. NAIRAC, Brit. J. Ophth. **31: 100** (Nov.) 1947.

A Negro woman, aged 22, two weeks prior to consultation felt a strong, burning pain in the right eye, followed by a discharge of "pus." The following day the left eye became similarly affected. Both eyes showed a prolapse of the iris between 11 and 1 o'clock. The holes in each cornea were clearcut, oval and placed just central to the corneoscleral junction. There was no evidence of inflammation. The fundi were normal. The whole of the prolapsed iris was cauterized and a thick conjunctival flap placed over the area. The probable explanation of the condition is a bilateral acute infection with formation of corneal ulcers, which, with the help of severe blepharospasm and rubbing, perforated quickly and healed.

W. ZENTMAYER.

Vision

THE COMPARATIVE VISUAL ACUITY AND EASE OF READING IN WHITE AND COLORED LIGHT. L. C. MARTIN and R. W. B. PEARSE, Brit. J. Ophth. **31: 129** (March) 1947.

The purpose of the experiments was to obtain information on the relative acuity of an accommodated eye both in red and in white light and on the comparative "ease of reading." The conditions imposed on the work precluded the use of artificial pupils, and binocular vision was used throughout. Careful attention was paid to the level of brightness of the visual field and the consequent state of adaption.

The general results indicate that, while there is a suggestion of improvement when red light is used rather than white at low levels of illumination, the answer to the question of the influence of chromatic aberration of the eye on acuity cannot be answered with any certainty, owing to the strong influence of intensity on acuity and the uncertainties of heterochromatic photometry.

The observation that intensity rather than color was the major controlling factor in acuity in the laboratory experiments suggested that when filters are used in conditions of high illumination acuity of vision might be similarly affected.

The most prominent feature of the observations is the loss of acuity with the majority of the filters; the loss is generally greater, the greater the absorption.

Tests made to establish the comparative "ease of reading" in red and in white illumination showed that any difference between the two illuminations in their effect on ease or speed of reading is too small to be established with certainty in the present experiments at levels of 0.3 and 6.0 foot candles, though there is indication that "white" light may have some advantage at the higher, and "red" light at the lower, of these two levels.

W. ZENTMAYER.

ANALYSIS OF BINOCULAR VISION. J. PLICQUE, Ann. d'ocul. **179: 83** (Feb.) 1946.

The author discusses the anatomy and physiology of the retina and the cerebral cortex with reference to the phenomena pertaining to binocular vision. Then follows a discussion of such topics as the uni-

ocular and binocular perception of depth, aniseikonia and the measurement of stereoscopic vision.

The article cannot be adequately summarized and should be read at length to be appreciated. P. R. McDonald.

Official Control of Color Vision in Sweden. C. G. Boström and I. Kugelberg, Ophthalmologica **114:** 95 (Aug.) 1947.

The official color tests in Sweden are made with the new pseudochromatic charts produced by Boström and Kugelberg, as well as the older ones of Göthlin and Boström. The Isihara and Stilling charts are no longer used, having been proved unreliable. If there is any abnormality of color sense, a second test is made with a spectrum.

F. H. Adler.

Fusion Frequency with Intermittent Light Under Various Circumstances. B. S. Hylkema, Acta ophth. **20:** 159, 1942.

The author's summary, in part, is as follows:

An investigation of the fusion frequency was made at various light intensities, especially at high intensities. In the fusion frequency–intensity curve, a peak is formed in the area of from 200 to 800 candle powers per square meter. It may be that this luminosity is the optimum for visual function, and perhaps the determination of fusion frequency can be used to ascertain ideal lighting conditions. O. P. Perkins.

Visual Tracts and Fields

Measurement of the Conductability of the Central Optic Pathway by Means of Combined Electroretinography and Electroencephalography. M. Monnier and R. L. Jeanneret, Ophthalmologica **113:** 1 (Jan.) 1947.

Simultaneous electroretinographic and electroencephalographic studies on human subjects enable the authors to divide "blocking time" of the alpha rhythm into two periods. The duration of the first (retinal time) extends from the onset of the light stimulation to the moment the impulses are discharged into the optic nerve. It corresponds to the latent period of potential b of the electroretinogram and varies with the intensity of the stimulation. The authors measured the retinal latent period and obtained a mean in the normal subject of 45 milliseconds. The second period (postretinal, or central, time) lasts 124 milliseconds in the normal subject. It corresponds to the conduction time of the impulses within the central optic pathways and is independent of the intensity of stimulation.

In a patient with tabetic atrophy of the optic nerve, the authors found a longer conduction time, namely 225 milliseconds in the right eye and 264 milliseconds in the left eye. These values were subject to greater variations in the patients with tabetic atrophy than in the normal subjects. The significance of these changes is discussed. F. H. Adler.

Sympathetic Ophthalmia

SYMPATHETIC OPTIC NEURITIS: REPORT OF A CASE. LEGROUX, Arch. d'opht. **6:** 43, 1946.

The case was that of a boy aged 15 who lost his left eye as the result of an accident. On first examination the eye was atrophic; it was enucleated but, unfortunately, was not examined histologically. Vision in the right eye was reduced to 0.10. The media were clear, and the nerve head presented the appearance of neuritis. The iris was normal. In the course of treatment a decompression of the sphenoid bone was done; after this, notable improvement in vision took place. Treatment consisted also of administration of sodium salicylate.

S. B. MARLOW.

Book Reviews

Strabismus—A Clinical Handbook. By George J. Epstein. Price, $5.00. Pp. 224, with 123 illustrations. Philadelphia: The Blakiston Company, 1948.

That this is the third book dealing with the ocular muscles to appear within a year points to the renewed interest in strabismus. The present volume has much to recommend it to all students, regardless of their degree of experience.

The section on anatomy and physiology of the extraocular muscles is generally good. There are a few minor mistakes which should be corrected in subsequent editions. Illustration 5, of the torsional movements of the globe, and the text on page 9 are incorrect. If movements of the right eye are considered alone, on looking up and to the right and on looking down and to the left, the right eye undergoes extorsion. On looking up and to the left or down and to the right, the eye undergoes intorsion. The after-images should occupy the same positions and correspond in their tilt to the tilt of the vertical meridian of the eye. Illustration 6, on page 10, is also wrong. It is stated that the figure was taken from Duke-Elder's "Text-Book of Ophthalmology," but it does not correspond to figure 583 in Duke-Elder's first edition, volume I, which illustration is correct.

Some sections of the book, particularly the physiology of binocular vision and those parts which deal with retinal correspondence, will not be acceptable to all students of squint. The author states that in monocular concomitant esotropia the phenomenon of monocular anomalous retinal correspondence "is always present," and that in alternating concomitant esotropia, alternating anomalous retinal correspondence "is always present." Just what is meant by "monocular" and "alternating anomalous correspondence" is not clear to the reviewer. The author can hardly mean to imply that all cases of concomitant strabismus have anomalous retinal correspondence. It would seem that he has this idea, however, since he describes normal retinal correspondence as a "sensory state existing in cases of normal muscle balance" and says, further, that when strabismus supervenes this state is altered and the alteration is known as anomalous retinal correspondence. This is an unorthodox point of view.

The author firmly believes that concomitant strabismus generally arises from a congenital muscle paresis and that the most common muscle affected with congenital paralysis is the superior rectus. This is another subject about which there has been much debate. The sections on treatment, especially the surgical treatment of strabismus, are clear and concise. The book is very readable. The style is reminiscent of Chavasse and therefore contrasts favorably with many of our American texts, in which the style is generally not fluent and is frequently awkward.

FRANCIS H. ADLER.

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